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ONCOLOGY OVERVIEW

Selected Abstracts on

Interferon: Preclinical Studies of Antiviral Activity

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Selected Abstracts
on

Interferon: Preclinical Studies of Antiviral Activity

William E. Stewart II, Ph.D.
Consulting Reviewer

A SERVICE OF THE INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM
OF THE NATIONAL CANCER INSTITUTE

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INTRODUCTION

This ONCOLOGY OVERVIEW on Preclinical Antiviral Activity of Interferons contains abstracts of literature published mainly from 1975 to 1981, with some earlier material included for historical perspective. All abstracts have been selected from the CANCERLIT computerized data base. The strategy used for this on-line literature search is available upon request from the CIDAC-VIB office, and can be entered at any MEDLARS/MEDLINE terminal system in order to obtain continuing updates on this topic.

The scope of this OVERVIEW includes the mechanisms by which interferons exert their antiviral effects, as well as studies of interferons' antiviral efficacy in vitro and in preclinical in vivo trials. Factors influencing sensitivity of viruses to interferons, agents which enhance or diminish interferons' antiviral activity, and host cell characteristics which influence sensitivity to interferons' antiviral activity are covered. Preclinical pharmacologic studies are also considered.

Related topics are covered in other ONCOLOGY OVERVIEWS in a series on Interferon. They include Interferon: Induction, Production and Physicochemical Properties; and Interferon: Preclinical Studies of Anticellular, Antitumor and Immunomodulatory Activity.

This OVERVIEW was prepared by William E. Stewart II, Ph.D. (editor), of the Interferon Laboratories, Memorial Sloan-Kettering Cancer Center, New York, N.Y., and Deborah Liss-Suter, B.A., of the CIDAC for Virology, Immunology and Biology, Franklin Research Center, Philadelphia, Pennsylvania.

EDITORIAL COMMENTARY

The interferon system, which includes the induction and action aspects of interferon, has expanded to include molecular biology, genetics, biochemistry and physiology for each of the interferon molecules and their various activities (1). The antiviral activity of interferons, the property first discovered for these proteins (2), is still used as the criterion for classification as an interferon. Thus, "to qualify as an interferon a factor must be a protein which exerts virus-nonspecific antiviral activity at least in homologous cells through cellular metabolic processes involving synthesis of both RNA and protein" (3). This ONCOLOGY OVERVIEW will deal exclusively with the literature pertaining to the in vitro and in vivo antiviral actions of interferons; the literature on the induction, production, purification and characterization of interferons and their other "non-antiviral" activities is covered in other volumes of the ONCOLOGY OVERVIEW series.

The antiviral activity induced in cells by interferon has certain general characteristics: it does not result from non-specific toxic effects on cells; the replication of a wide range of viruses is inhibited and development of the antiviral state requires de novo cellular protein synthesis (4,5); the relative sensitivities of viruses to interferon action differ according to the animal species of the interferon-treated cell (6,7), and the action mechanism against viruses can be manifested at several stages during the virus replication process, from early steps in processing of viral nucleic acids, to the packaging and release of virions.

The interferon-induced antiviral state has been reported to involve the inhibition of primary transcription in some cases (8) and translation in all cases (9). Extensive studies of the mechanism of the translation inhibition induced by interferon have revealed that interferon-treated cells, in the presence of double-stranded RNA (presumably provided in infected cells by the initiation of viral replicative processes), invest energy (ATP) into the direct activation of two enzymes: a kinase, and a synthetase. The activated kinase then phosphorylates a ribosomal initiation factor, eIF-2, thereby inhibiting messenger RNA translation by preventing its initiation (10,12). The activated synthetase generates an unusual oligonucleotide with the structural formula pppA2'p5'A2'p5'A((2'-5')An) which is able in turn to activate a third enzyme in interferon-treated cells, an endonuclease, which degrades both cellular and viral messenger RNAs (13).

Some viruses which are apparently able to begin replication and produce double-stranded RNA in interferon-treated cells are unable to complete their replication because the host cell disin-

tegrates (14). This abortive infection mechanism appears related to the enhanced susceptibility of interferon-treated cells to the toxicity of double-stranded RNA (15).

Some viruses may be inhibited at even later stages in their replicative process. Interferon-induced cell membrane alterations may inhibit virus release; certain components of RNA tumor viruses have been found to accumulate in interferon-treated cells (16,17). Additionally, physical alteration of the virions of both RNA tumor viruses (18) and non-tumor budding viruses (19) produced by interferon-treated cells are noted. These defective virus particles can then interfere with subsequent cycles of virus infection and replication.

In animal systems, interferon's multiple mechanisms of muting virus multiplication are amplified by its enhancement of various immune functions, including cytotoxicity of antibodies and lymphocytes, phagocytosis, macrophage activation and antibody response. The combined antiviral and non-antiviral activities may explain findings that the in vivo sensitivity of a virus to interferon does not necessarily correlate with its sensitivity in vitro (20). In addition, endogenously induced interferon has usually been found to be more effective than exogenously administered interferon against virus infections in animals. Thus, the "antiviral actions" of interferons seem to operate at a number of levels in vitro as well as in vivo.

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ABSTRACTS

I. MECHANISMS OF ANTIVIRAL ACTION OF INTERFERONS

A.

Effects of Interferons on Virus Attachment, Penetration and Uncoating

1. EFFECT OF INTERFERON ON THE UNCOATING OF MURINE LEUKEMIA VIRUS AFTER EXOGENOUS INFECTION (MEETING ABSTRACT).

Shoor R, Aboud M, Salzberg S
Bar-Ilan Univ., Ramat Gan, Israel
Isr J Med Sci; 15(1):64-65 1979

Previous experiments have indicated that interferon (IF) interferes with some early steps of exogenous murine leukemia virus (MLV) infection which occur before the integration of viral DNA into the host genome. We now demonstrate that one of the early steps affected by IF is the viral uncoating. While penetrating virus appears to be uncoated rapidly in untreated cells, it remains intact for at least 105 min in the cytoplasm of IF-treated cells. The uncoating process is demonstrated by analyzing reverse transcriptase activity present in the cytoplasm of infected cells in sucrose gradients. Thus, when cells are incubated with MLV for various times, particulated virion accumulated in the IF-treated cells to a much higher level than in untreated cells. (no Refs)

2. EFFECT OF INTERFERON ON THE INITIAL STEPS OF EXOGENOUS INFECTION OF MURINE LEUKEMIA VIRUS (MEETING ABSTRACT).

Aboud M, Shoor R, Moldovan D, Salzberg S
Fac. Pub. Health Science, Ben-Gurion Univ., Beer-Sheva, Israel
Abstracts of the 12th Meeting of the European Tumor Virus Group, held in Belgium, September 10-14, 1979, 1979.

This study concerns the effect of interferon (IF) on the adsorption, uncoating and subsequent viral DNA synthesis of murine leukemia virus (MLV). NIH/3T3 mouse fibroblasts, either untreated or treated with 80 units/ml of IF, were infected with 3 plaque-forming units/cell of MLV. Virus adsorption was estimated by analysis of viral reverse transcriptase activity in the cell membrane and was found to be unaffected by IF. Virus uncoating was followed by detecting intracellular virions from the cell cytoplasm. This process was found to be delayed for 2-3 hr in IF-treated as compared to untreated cells. The IF-mediated inhibition of viral uncoating appeared to result from its interaction with the cell membrane, since 30 min of IF treatment in the presence of cycloheximide was sufficient to produce this effect. Viral cytoplasmic DNA synthesis was found to reach max level at 3.5 hr after infection, followed by a gradual decline. The amount of viral DNA synthesized during this initial period was much lower in IF-treated cells. This inhibitory effect was observed even when cells were treated with IF for only 30 min, suggesting that it reflected the consequences of IF effect on viral uncoating. This conclusion was further supported by the finding of a second burst of viral DNA synthesis in the IF-treated cells occurring at a later stage of the infectious cycle of MLV. (no Refs)

3. INTERFERON INHIBITS TRANSFORMATION BY MURINE SARCOMA VIRUSES BEFORE INTEGRATION OF PROVIRUS.

Avery RJ, Norton JD, Jones JS, Burke DC, Morris AG
Dept. Biological Sciences, Univ. Warwick, Coventry CV4 7AL, England
Nature (Lond); 288(5786):93-95 1980

Interferon (IF)-induced inhibition of neoplastic transformation by C-type viruses was studied in five cell clones isolated in the presence of IF from murine fibroblasts that had been treated with IF and then infected with Kirsten strain murine sarcoma virus (KiMSV). Integration of the KiMSV provirus into the cellular genome of these clones was investigated by hybridization experiments using DNA complementary to purified KiMSV RNA and by restriction enzyme analysis using the Southern blotting technique. Results obtained in both of these types of experiments indicated that the cellular genomes of the IF clones did not contain integrated KiMSV proviral DNA. The possibility that IF may prevent transformation by inhibiting adsorption or penetration of the virus was investigated by determining the effect on KiMSV transformation of IF added after infection. The results of these experiments showed that IF added 4 hr after virus infection was as effective in blocking transformation as IF added before infection; some IF sensitivity was still seen in cultures treated with IF 24 hr after infection. These data indicated that IF did not act by inhibiting adsorption, penetration, or uncoating of the virus; an extension of these experiments indicated that IF acts at or after provirus synthesis. It was concluded that IF blocks infection by C-type viruses at a stage after uncoating but before integration of the provirus. (21 Refs)

B.

Effects of Interferons on Viral Nucleic Acid Transcription

4. INTERFERON ACTION III. THE RATE OF PRIMARY TRANSCRIPTION OF VESICULAR STOMATITIS VIRUS IS INHIBITED BY INTERFERON ACTION.

Marcus PI, Sekellick MJ
Microbiology Section, U-44, Biological Sciences Group, Univ. Connecticut, Storrs, CT, 06268
J Gen Virol; 38(2):391-408 1978

Transcription of vesicular stomatitis virus (VSV) in Vero cells was confined to the synthesis of parentally-derived messenger RNA (mRNA) (primary transcription) by the use of cycloheximide and/or a temperature sensitive (ts) mutant, G41(IV), at a non-permissive temperature (40 C). More transcripts accumulated in the presence of cycloheximide than in its absence. This so-called 'cycloheximide effect' results from higher rates of virus transcription sustained for longer periods of time. The rate of VSV transcription ini-

tially increases linearly for 1 to 2 hr after infection. Interferon reduces this rate (approx fourfold with 50 units/ml interferon) irrespective of the presence or absence of cycloheximide. The VSV mRNA transcripts synthesized in mock- or interferon-treated cells were equal in size and had an equivalent half-life of 17 hr at 40 C. It seems likely that once transcription is initiated in interferon-treated cells, it is completed successfully. Since interferon reduces the rate of early VSV primary transcript synthesis to below that achieved in the presence of cycloheximide, we conclude that interferon has an effect on transcription beyond that attributable solely to protein synthesis inhibition. We postulate that interferon decreases the probability of initiating virus transcription. Virus mRNA escaping this facet of interferon action may then encounter other facets such as post transcriptional modification and/or inhibition of translation. However, the mandatory sequence of primary transcription to primary translation for negative-strand viruses like VSV dictates that the overall inhibitory effect of interferon on translation would derive in part from this prior inhibition of transcription. Thus, to apply the term 'primary effect' to one particular facet of interferon action may not always be meaningful. (Author abstract) (45 Refs)

5. CELL KILLING BY VIRUSES: THE INTERFERON SYSTEM AND INHIBITION OF CELL KILLING BY VESICULAR STOMATITIS VIRUS.

Marcus PI, Sekellick MJ

Microbiology Section, U-44 Biological Sciences Group, Univ. Connecticut, Storrs, CT 06268

Virology; 69(2):378-393 1976

The host response of cell killing particle (CKP) activity of vesicular stomatitis virus (VSV) in green monkey kidney Vero cells treated with interferon or in mouse L cells treated with poly(rI);poly(rC) was determined from single-cell survival curves, and compared with dose-response curves for infectivity and viral transcript accumulation. "Pulse-infection" with temperature-sensitive (ts) mutants of VSV was used to confine formation of putative cell killing factor or its precursors to the time equivalent of a single cycle of growth. Cells which through interferon or poly(rI);poly(rC) action survived a pulse-infection with ts-mutant virus at permissive temperature produced colonies normal in both appearance and growth rate. Cells treated with interferon or poly(rI);poly(rC) and challenged with VSV generated a family of survival curves for CKP activity whose slopes decreased as the dose of the interferon-interference inducer increased. These curves revealed that the capacity to express CKP activity or accumulate transcripts in interferon-treated Vero cells was lost initially at an exponential rate four to five times slower than that observed for the loss of plaque or yield reducing capacity, hence it required four to five times more interferon to prevent cell killing or *transcript accumulation* by VSV than was needed to reduce infectivity by an equivalent amount. A marked tailing of the survival curves was observed as the interferon dose was increased, resulting in surviving activity for CKP and transcript accumulation in the excess of that expected by extrapolation. The previous hypothesis had stated that viral transcription was a requisite, though insufficient reaction to produce cell killing by VSV and that integrity of about one-fifth of the viral genome sufficed to provide these transcripts. We extend this and propose that lethal action of VSV on cells requires: (i) functional virion transcriptase, (ii) transcription of a special one-fifth of the genome, most likely coding for proteins N and NS, (iii) translation of these transcripts into minimally functional polypeptides which lead to (iv) formation and subsequent action by a putative cell killing factor.

6. EFFECT OF INTERFERON ON TRANSCRIPTION AND TRANSLATION OF VESICULAR STOMATITIS VIRUS IN HUMAN AND SIMIAN CELL CULTURES.

Thacore HR

Dept. Microbiology, Sch. Medicine, State Univ. New York at Buffalo, Buffalo, NY, 14214

J Gen Virol; 41(2):421-426 1978

The effect of interferons on vesicular stomatitis virus (VSV) primary transcription, amplified RNA synthesis (ie the sum of primary transcription RNA replication (leading to (-) RNA) and secondary transcription (leading to (+) RNA)) and virus protein synthesis was studied. In a human cell line, both human and simian interferons inhibited the initiation of primary transcription and amplified RNA synthesis. In contrast, in a simian cell line tested similarly, the initiation of these activities was not affected, though they decreased as the infection progressed. Nevertheless, virus protein synthesis was completely inhibited. These results demonstrate that the action of interferon on virus transcription and/or translation may depend more on the host cell than on the particular interferon used. (Author abstract) (19 Refs)

7. INHIBITION OF RNA AND PROTEIN SYNTHESIS IN INTERFERON-TREATED HELA CELLS INFECTED WITH VESICULAR STOMATITIS VIRUS.

Simili M, De Ferra F, Baglioni C

Dept. Biological Sciences, State Univ. New York (Albany), Albany, NY, 12222

J Gen Virol; 47(2):373-384 1980

Synthesis of vesicular stomatitis virus RNA and protein is almost completely inhibited in HeLa cells treated with relatively high doses of human fibroblast interferon. With lower concentrations of interferon virus replication is inhibited, but near normal amounts of virus RNA are found in these cells with the exception of genomic-size RNA. In contrast, synthesis of all the virus proteins is equally inhibited in proportion to the interferon concentration used to treat the cells. This inhibition is due to a decline in the rate of protein synthesis, which occurs in interferon-treated cells sooner after infection than in untreated cells. The decreased rate of protein synthesis is accompanied by a change in the polysome pattern of infected cells, characterized by polysome run-off and increase in 80S ribosomes. At the same time, a larger proportion of the virus poly(A)-containing RNA is not associated with polysomes in interferon-treated cells than in control cells. The non-polysomal virus RNA has a sedimentation rate identical with that of polysomal virus RNA. Possible causes for the decline in the rate of protein synthesis observed in interferon-treated cells are discussed. (Author abstract) (24 Refs)

8. 2'5'OLIGO(A) POLYMERASE ACTIVITY AND INHIBITION OF VIRAL RNA SYNTHESIS IN INTERFERON-TREATED HELA CELLS.

Baglioni C, Maroney PA, West DK

Dept. Biological Sciences, State Univ. New York, Albany, NY, 12222

Biochemistry (Washington); 18(9):1765-1770 1979

A quantitative assay for 2'5'oligo-adenylic acid (A) polymerase, based on the adsorption of cell extract to polyinosinic acid-polycytidylic acid-agarose and incubation with [3H]ATP, has been developed. The [3H]2'5'oligo(A) synthesized is resolved from ATP by chromatography on diethylaminoethyl-cellulose. The 2'5'oligo(A) polymerase activity has been measured in extracts of control HeLa cells and cells incubated with different concentrations of human fibroblast interferon or for different lengths of time with 100

units/ml of interferon. An increased enzymatic activity can be detected in cells treated with 12.5 units/ml or higher concentrations for 17 hr and in cells treated with 100 units/ml longer than 3 hr. The synthesis of encephalomyocarditis virus (EMC) RNA is inhibited in these cells in parallel with the increase in polymerase activity. Treatment of HeLa cells with interferon followed 2 hr later by actinomycin D prevents the increase in 2'5'oligo(a) polymerase and the inhibition of viral RNA synthesis. After 4-hr treatment with interferon, actinomycin D does not show this effect, whereas cycloheximide prevents the increase in polymerase activity. Active RNA synthesis 2 hr after the start of interferon treatment and active protein synthesis 4 hr afterward is necessary for the increase in 2'5'oligo(A) polymerase activity. Another enzymatic activity, previously reported to be increased in interferon-treated cells, is a double-stranded RNA activated protein kinase, which phosphorylates two polypeptides associated with ribosomes. Assays of this protein kinase have shown an increase in activity in cells treated with 12.5 units/ml or higher interferon concentrations. However, the increase in kinase activity can only be detected in cells treated for at least 10 hr. In particular, HeLa cells treated for 7 hr with 100 units/ml of interferon do not show increased protein kinase activity; upon such treatment, EMC RNA synthesis is already significantly inhibited. Therefore, an increased protein kinase activity may not be required for an inhibition of EMC RNA synthesis. (Author abstract) (23 Refs)

9. CYTOPLASMIC VIRAL DNA SYNTHESIS IN EXOGENOUS INFECTION OF MURINE LEUKEMIA VIRUS: EFFECT OF INTERFERON AND CYCLOHEXIMIDE.

Aboud M, Moldovan-Levin D, Salzberg S
Microbiology and Immunology Unit, Faculty of Health Sciences, Ben-Gurion Univ. Negev, Beer-Sheva, Israel
J Virol; 37(2):836-839 1981

Cytoplasmic viral DNA synthesis can be followed efficiently by [3H]thymidine labeling of cells exogenously infected with Moloney murine leukemia virus. Both the negative and the positive strands of viral DNA reached their max level in the cytoplasm at 3.5 hr postinfection. Interferon treatment before infection markedly reduced the amount of viral DNA formed during the first 3.5 hr, but led to a second major wave of viral DNA synthesis, peaking at 7.5 hr postinfection. No such late cytoplasmic DNA synthesis occurred in the untreated control. Inhibition of protein synthesis by cycloheximide, on the other hand, stimulated cytoplasmic viral DNA synthesis during the first 3.5 hr. (Author abstract) (23 Refs)

10. CHARACTERIZATION OF INTRACELLULAR VIRAL RNA IN INTERFERON-TREATED CELLS CHRONICALLY INFECTED WITH MURINE LEUKEMIA VIRUS.

Salzberg S, Bakhanashvili M, Bari S, Berman I, Aboud M
Dept. Life Sciences, Bar-Ilan Univ., Ramat-Gan, Israel
J Virol; 35(3):694-703 1980

We have recently found that Moloney murine leukemia virus assembles within cytoplasmic vacuoles of chronically infected NIH/3T3 cells rather than at their surface. In the present study we found that if these cells were treated with interferon (IF) for 24 to 48 hr, the intracellular virus particles accumulated at a two- to three-fold higher level than that observed in untreated cells. Nevertheless, despite this accumulation, no difference between IF-treated and untreated cells was observed in the amount of the total cytoplasmic viral RNA or in its 35S or 21S species. When cellular virions were sedimented from the cytoplasmic fraction, a markedly higher amount of viral RNA was detected in the viral pellet of IF-treated cells than was detected in untreated cells, whereas the amount of viral RNA left in the virus-free cytoplasm of IF-treated cells was much lower than that in the untreated cells. Furthermore, the amount of the cytoplasmic polyriboadenylic acid-containing viral RNA was also remarkably higher in the IF-treated cells. Viral polyribosomes appeared to be fully functional in IF-treated cells, since no effect of IF on viral protein synthesis could be detected. Analysis of the nuclear viral RNA showed no difference between IF-treated and untreated cells after 24 hr of IF treatment. Both contained a comparable amount of 35S viral RNA. However, at 48 hr a significant accumulation of viral RNA was observed in the nucleus of the IF-treated cells as compared with the untreated cells, although in both cases only 35S species were evident. This accumulation appeared to activate a degradation process which destroyed nuclear viral RNA, since a dramatic shift toward smaller-sized molecules of viral RNA and a remarkable reduction in its amount were observed after 72 hr of IF treatment. (Author abstract) (43 Refs)

11. EFFECT OF INTERFERON ON CHRONIC AND EXOGENOUS INFECTION OF CELLS WITH MURINE LEUKEMIA VIRUS (MEETING ABSTRACT).

Salzberg S, Abound M, Bakhanashvilli M, Shoor R
Bar-Ilan Univ., Ramat-Gan, Israel
J Clin Hematol Oncol; 9(4):283 1979

The effect of interferon (IF) on the properties of intracellular viral RNA was studied in NIH/3T3 cells chronically infected with murine leukemia virus (MLV). An accumulation of 35 S (Svedberg units) viral RNA molecules occurred in the nucleus of IF-treated cells at 48 hr of IF-treatment, followed by a degradation process which resulted both in a decreased amount and in smaller size molecules of viral RNA present in the nucleus at 72 hr of IF-treatment. No difference either in the amount or size of cytoplasmic viral RNA could be demonstrated at 48 hr of IF-treatment. However, the amount of viral RNA detected in intracellular virions present in IF-treated cells was about twice that detected in untreated cells. Moreover, the amount of polyadenylated cytoplasmic viral RNA in IF-treated cells was found to be twice that of untreated cells. Thus, a significant difference in the properties of cytoplasmic viral RNA exists between IF-treated and control cells. The effect of IF on NIH/3T3 cells exogenously infected with MLV was also studied. The uncoating of virions was clearly inhibited by IF-treated cells. This inhibition was not a result of the cellular IF-induced antiviral state since it occurred with the same efficiency in cells treated with IF in the presence of cycloheximide or in cells treated with human IF. (no Refs)

12. EFFECT OF INTERFERON ON EXOGENOUS MURINE LEUKEMIA VIRUS INFECTION.

Aboud M, Shoor R, Salzberg S
Dept. Life Sciences, Bar-Ilan Univ., Ramat-Gan, Israel
Virology; 84(1):134-141 1978

When NIH/3T3 cells were treated with interferon (IF: at a dose resulting in a 50% reduction of reverse transcriptase activity) before infection with Moloney murine leukemia virus (M-MLV: 1 plaque-forming unit/cell), no significant release of viral progeny occurred as long as IF remained in the medium. This was not due to inhibition of virus replication or to interference with virus penetration, since M-MLV release returned to control levels when IF was removed prior to or 6 hr after infection. Furthermore, IF had no effect on the formation of infectious centers. IF *reduced*

viral RNA synthesis, as did the protein synthesis inhibitor cycloheximide (10 microg/ml) when it was added early after infection. When added for 5-9 hr postinfection, the drug had no effect on RNA synthesis. When IF was eliminated from pretreated cultures up to 10 hr before M-MLV infection, progeny release was still affected. These results demonstrate that IF exerts its effect at the early stage of exogenous MLV infection. (30 Refs)

13. EFFECTS OF INTERFERON ON BIOCHEMICAL EVENTS ASSOCIATED WITH THE REPLICATION OF RNA TUMOR VIRUSES (MEETING ABSTRACT).

Salzberg S, Shurtz R, Moldovan D, Aboud M
Bar-Ilan Univ., Ramat Gan, Israel
Isr J Med Sci; 15(1):104 1979

NIH/3T3 cells were infected with three plaque-forming units of murine leukemia virus (MLV) and treated for 2-hr periods with 20 ug/ml of puromycin immediately following infection. Virus production was followed by reverse transcriptase (RT) activity present in the culture medium. A significant inhibition in virus production was detected in puromycin-treated cells. Viral RNA containing polyadenylic acid was detected in polyribosomes between 1 and 4 hr after infection, with the greatest abundance at 3 hr. In the free cytoplasm, however, the greatest abundance of viral RNA was detected at the first 2 hr after infection, followed by a decrease. Small amounts of viral RNA were also found in uninfected cells. In experiments aimed at understanding the mechanism of the inhibition of MLV production by mouse interferon, it was established that, whereas viral RNA synthesis has been inhibited in exogenously infected cells after mouse interferon treatment, in chronically infected cells an accumulation of viral RNA was detected in the nuclei at 48 hr after addition of mouse interferon. (no Refs)

14. NUCLEIC ACID AND PROTEINS ISOLATED FROM A STRAIN OF MURINE SARCOMA VIRUS (MEETING ABSTRACT).

Horvath AE, Friedman RM
Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.
Proc Soc Exp Biol Med; 137(3):1075-1081 1971

Murine sarcoma virus (MSV-O, Moloney) was grown in tissue cultures of transformed rat cells (MSB-1). The media containing the virus particles were collected and the virus purified by sucrose density gradient ultracentrifugation. The buoyant density of the purified virus was 1.16 g/ml. The incorporation of 3H- uridine was shown to be reduced in virus preparation from cells treated with a crude rat interferon preparation, when compared to controls. In tissue cultures treated with a 1:3 dilution of *interferon*, the incorporation of 3H-uridine was reduced to about 35% of the control. In cells treated with a 1:10 interferon dilution a depression to 60% of the control was observed. Viral nucleic acid was extracted by the SDS phenol method and characterized by sucrose density ultracentrifugation. A sedimentation value of 52S or 64S was obtained, depending on the reference values used. Heating the viral RNA to 80 C caused it to dissociate into a major 32S and minor smaller S value species, suggesting that the larger RNA is either an aggregate of smaller 32S units, or that modifications had taken place in the secondary structure of the RNA. Pancreatic ribonuclease treatment disclosed no ribonuclease-resistant RNA in the virus or in the MSB cells. This is believed to confirm the single-stranded nature of viral RNA. Six proteins were extracted from purified MSV-O solubilized and separated by polyacrylamide gel electrophoresis.

15. THE EFFECT OF INTERFERON ON THE EARLY FUNCTIONS OF SIMIAN VIRUS 40.

Mozes LW, Defendi V
Dept. Pathology, New York Univ. Sch. Medicine, New York, NY, 10016
Virology; 85(1):315-318 1978

The ability of interferon (IF) to interfere with the penetration and uncoating of simian virus 40 (SV40) was studied by monitoring the inhibition of SV40-induced tumor antigen (T Ag) in permissive TC7 monkey cells and nonpermissive mouse embryo fibroblasts. Addition of IF to cells previously transformed by SV40 had no effect on T Ag production. However, pretreatment of cells with homologous IF 20 hr prior to SV40 injection resulted in a dose-dependent decrease in the proportion of T Ag-positive cells at 48 hr postinfection. IF addition at increasingly later times after SV40 injection resulted in a progressive reduction in T Ag-positive cells; the sensitivity to inhibition by IF was lost by 12 hr after infection. Penetration and uncoating of SV40 were ruled out as the major site of IF action, since the induction of T Ag by infectious DNA extracted from SV40 virions was also sensitive to IF treatment. Furthermore, addition of IF to cells did not result in resistance to viral infection until several hours had elapsed. These findings suggest that the inhibitory effect of IF is primarily at a step between SV40 uncoating and integration of viral DNA into the host cell genome. (16 Refs)

16. INTERFERON INHIBITS THE IN VITRO ACCUMULATION OF VIRUS SPECIFIC RNA IN NUCLEI ISOLATED FROM SV40 INFECTED CELLS.

Metz DH, Oxman MN, Levin MJ
Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England
Biochem Biophys Res Commun; 75(1):172-178 1977

The mechanism by which interferon (IF) inhibits simian virus 40 (SV40) replication was investigated using an in vitro system consisting of nuclei from infected Vero cells that in the presence of cytosine arabinoside synthesize early SV40 RNA. The in vitro synthesis of SV40-specific RNA was almost completely blocked by low doses of d-amanitin, but total RNA synthesis was only partially inhibited. The accumulation of viral RNA was blocked in nuclei prepared from cells pretreated with IF prior to infection and incubated in a reaction mixture containing 100 milliM KCl. This resembled the situation in intact cells. When the reaction mixture contained 300 milliM KCl, however, the IF-induced block in viral RNA accumulation was reversed. Two possible explanations are offered for the effect of IF treatment on the accumulation of early viral transcripts in SV40-infected cells. First, IF treatment may induce the formation of an intracellular inhibitor that blocks viral transcription; elevated salt concentrations in vitro might then displace the inhibitor and permit transcription of the viral genome. Second, the reduced accumulation of early viral RNA may be due to enhanced degradation within the nucleus of the IF-treated cell effected by a ribonuclease specific for viral, but not for most cellular RNA. This putative nuclease might be inactivated at elevated ionic strength, resulting in the increased level of SV40-specific RNA seen in nuclei incubated with 300 milliM KCl in vitro. These two possibilities cannot be distinguished at present. (14 Refs)

17. MECHANISM OF INTERFERON ACTION: FURTHER EVIDENCE FOR TRANSCRIPTION AS THE PRIMARY SITE OF ACTION IN SIMIAN VIRUS 40 INFECTION

Metz DH, Levin MJ, Oxman MN
Natl. Inst. for Medical Res., Mill Hill, London NW7 IAA, England
J Gen Virol; 32(2):227-240 1976

Simian virus 40 (SV40) is used to investigate the action of interferon. Early SV40 RNA was prepared by infecting African-green-monkey kidney cells with 30 to 100 plaque-forming units (pfu) of SV40 per cell. The protein synthesis inhibitors cycloheximide (7.5 to 15 ug/ml) and p-fluorophenylalanine (25 ug/ml) were added 1 hr before, or at the time of, infection. Another cell sample was incubated with interferon for 18 hr and then infected with SV40 at a multiplicity of 50 to 100 pfu/cell. In both cases the amount of early SV40 RNA had decreased by 90 to 95% a day later, but there was no reduction in uncoated SV40 DNA. Total SV40 DNA was measured in interferon-treated and in control samples; no significant difference was found. These experiments indicate that the observed reduction of early SV40 RNA in interferon-treated cells is not due to inhibition of the entry of the virus into the cell or of its subsequent transport to, and uncoating in, the nucleus or to an increase in the rate of degradation of uncoated SV40 template in the nucleus. The primary effect of interferon on SV40 appears to be the inhibition of the transcription of early virus RNA or the enhancement of its turnover in the nucleus. Since in other virus systems interferon acts by inhibiting translation, there must be at least two methods by which interferon acts on viruses. (44 refs)

18. MOLECULAR MECHANISMS OF THE ANTIVIRAL ACTION OF INTERFERON: EFFECTS OF INTERFERON ON THE TRANSCRIPTION OF VIRAL MESSENGER RNA.

Oxman MN
Dept. Medicine and Pathology, Univ. California, San Diego, CA
Tex Rep Biol Med; 35:230-238 1977

Evidence from a number of virus-cell systems, discussed here and in other literature, shows that the resistance to virus infection induced by interferon is characterized by inhibition of both primary transcription and translation. This may be because interferon induces two (or more) distinct 'antiviral proteins' which inhibit, respectively, the transcription and the translation of virus genetic information. Although both may be present in interferon treated cells, the one which is manifest in any given experimental system may depend on whether transcription or translation is the primary event in the replication of the particular virus, and upon the accessibility of the viral nucleic acid. Alternatively, inhibition of transcription and translation may be mediated by a single antiviral protein which is able to distinguish viral from cellular nucleotide sequences in both DNA and RNA. The interferon-induced ribosome-associated inhibitors of viral messenger RNA translation are prime candidates for such an antiviral protein. (Author abstract) (27 Refs)

19. INTERFERON AND TRANSCRIPTION OF EARLY VIRUS-SPECIFIC RNA IN CELLS INFECTED WITH SIMIAN VIRUS 40 (MEETING ABSTRACT).

Oxman MN, Levin MJ
Harvard Med. Sch., Boston, Mass.
Proc Natl Acad Sci USA; 68(2):299-302 1971

African green monkey kidney cells (AGMK) and Vero monkey cells were infected with SV40 and treated with interferon prepared from human leukocytes and/or from AGMK cells. Human interferon reduced SV40 T antigen formation by 66% in AGMK cells and by 96% in Vero cells. Monkey interferon reduced SV40 T antigen formation by 96% in Vero cells when added to cultures in amounts of 20 U/ml and by 99% when added in amounts of 50 U/ml. In addition, virus-specific RNA (cRNA), as measured by either the proportion of input RNA hybridizing with SV40 DNA or by the total SV40 content of RNA hybridizing to a complementary DNA, appeared markedly reduced in cultures treated with interferon. SV40 cRNA was reduced 54% in AGMK cells treated with human interferon and 82% in Vero cells treated with human interferon. AGMK interferon reduced SV40 cRNA in Vero cells by 92%.

20. INHIBITION OF SIMIAN VIRUS 40 REPLICATION BY INTERFERON TREATMENT LATE IN THE LYTIC CYCLE.

Yakobson E, Revel M, Winocour E
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
Virology; 80(1):225-228 1977

Inhibition of simian virus 40 (SV40) replication by interferon treatment late in the lytic cycle is reported. The BSC-1 line of African monkey cells was exposed to homologous interferon both before and at different times after infection with SV40. Cultures were exposed to 100 units/ml of interferon at 24 hr postinfection. In both BSC-1 and CV-1 cells, interferon treatment after the onset of viral DNA synthesis resulted in a substantial inhibition of subsequent rounds of viral DNA replication. The inhibitory effect was first detected at about 12 hr after exposure of the cells to interferon. Interferon (100 units/ml) was found to be equally effective whether applied before infection or at 20 and 30 hr postinfection. Application of interferon at 42 hr postinfection, however, produced no detectable effect on SV40 DNA synthesis measured 6 hr later. When the yield of infectious virus at 80 hr postinfection was measured, the SV40 yield when interferon was added 28 hr postinfection (3.5 x 10 plaque forming units (PFU)/ml) was about the same as the SV40 yield when interferon was added 18 hr before infection (4 x 10 PFU/ml). Labeling experiments with H-thymidine indicated that the inhibition of SV40 DNA replication by interferon late in the infectious cycle operates primarily at the level of initiation of viral DNA synthesis. The lytic SV40-monkey cell system thus differs from other lytic virus-cell systems where the antiviral state develops maximally only when interferon is applied prior to infection. (13 Refs)

21. MECHANISM OF INTERFERON-INDUCED INHIBITION OF EARLY SIMIAN VIRUS 40 (SV40) FUNCTIONS.

Yamamoto K, Yamaguchi N, Oda K
Dept. Tumor Virus Res., Inst. Med. Sci., Tokyo, Japan
Virology; 68(1):58-70 1975

An investigation of the mechanism of interferon-induced inhibition of early simian virus 40 (SV40) function is described. Interferon was prepared by Newcastle disease virus infection of G9186 cells (a passaged culture of African green monkey kidney (AGMK) cells), and its activity was assayed by plaque reduction of vesicular stomatitis virus (VSV). Pretreatment of G9186 cells with interferon (4 units/ml) completely inhibited VSV plaque formation, while lesser sensitivity was observed with AGMK cells and other established lines (C14, GC7, T22, CV-1, and Vero). In terms of efficiency of T-antigen formation following SV40 infection, the G9186 cell line was again the most sensitive to interferon inhibition, although only at relatively high infective multiplicity. Similar dose-dependent inhibition was observed for synthesis of viral DNA and virally induced cellu-

lar DNA when secondary cultures of AGMK cells were pretreated with interferon (up to 300 units/ml), suggesting interferon acts at an early stage of infection. The complete inhibition of mRNA synthesis in GC7 cells pretreated with interferon (320 units/ml) and infected with SV40 at low multiplicity (4 PFU/cell) was partially overcome at high multiplicity (100 PFU/cell), and similar effects on T-antigen formation were seen. In addition, while the synthesis of cellular DNA in nonpermissive murine C3H2K-C4 cells pretreated with murine interferon (1000 units/ml) was reduced to 50% of control following infection at 15 PFU/cell, almost no inhibition was observed in cells infected at 100 PFU/cell. It was also found that SV40-DNA was unable to replicate in SV40-transformed monkey cells (T22) pretreated with interferon (160 units/ml), indicating lack of complementarity with early gene products present in the transformed cells. The synthesis of SV40-DNA and SV40-mRNA and the formation of T- and V-antigens were all much less inhibited by interferon (320 units/ml) in G9286 cells infected with the infectious DNA (0.75 ug/culture), compared with cells infected with SV40 virions. The 20-50% decrease in macromolecular synthesis was attributed to inefficient penetration of DNA into cell nuclei following interferon treatment, while there was no evidence for specific DNase or RNase induction. The results were consistent with interferon-induced inhibition of viral genome transcription and not inhibition of the translation of early and late mRNA. (37 refs)

22. INTERFERON-MEDIATED CHANGES IN THE METHYLATION PATTERN OF SIMIAN VIRUS 40 MESSENGER RNA (MEETING ABSTRACT).

Yakobson E, Kahane H, Revel M, Groner Y
Weizmann Inst. Science, Rehovot, Israel
Isr J Med Sci; 15(1):101 1979

We have recently shown that addition of interferon late in the lytic cycle of simian virus 40 (SV40) induces a block in virus replication at the post-transcriptional level. Although several translational inhibitors are induced by interferon, changes in the methylation pattern of viral messenger RNA (mRNA) may also contribute to the observed preferential inhibition of viral protein synthesis. To test this possibility, SV40 infected interferon-treated monkey BSC-1 cells were labeled with [methyl-3H]methionine for 6-8 hr. Labeled polyadenylate containing mRNA was isolated from the cytoplasm, and SV40-specific mRNA were selected by preparative hybridization to and elution from SV40 DNA. Selected RNA was extensively digested with P1 nuclease and bacterial alkaline phosphatase. Cap structures m7Gpppm6Am were separated from internal m6A residues by high-voltage electrophoresis. The ratio of methyl-3H radioactivity in caps vs m6A was determined. It was found that SV40 RNA extracted from interferon-treated cells has a three- to sixfold higher ratio of m6A to cap. Double-labeling experiment with [14C]uridine and [methyl-3H]methionine indicates that there is no reduction of methyl-3H radioactivity in the caps of viral RNA, but rather an increase in the methylation of m6A in the body of SV40 RNA is responsible for the observed increase in m6A/cap ratio. Labeling of viral RNA with [32P]orthophosphate also indicates that cap formation is not reduced in interferon-treated cells. (no Refs)

23. CYTOSINE ARABINOSIDE- AND INTERFERON-MEDIATED CONTROL OF POLYOMA AND SV40 GENOME EXPRESSION.

Brandner G, Mueller N
Tumor Viruses Cold Spring Harbor Symposia on Quantitative Biology. vol. 39, Cold Spring Harbor Lab. (Cold Spring Harbor, NY, 1975.

Studies on African green monkey kidney cells infected with polyoma and SV49 (777) indicated that SV40 transcription is primarily affected by interferon. However, interferon and cytosine arabinoside also inhibited the host DNA replication. This interruption has no effect on the current transcription of the late viral genes, indicating that the onset of viral DNA replication is a prerequisite for the persistence of the late SV40 and polyoma genome transcription.

24. INTERFERON-SENSITIVITY OF THE ENHANCED INCORPORATION OF THYMIDINE INTO CELLULAR DNA INDUCED BY POLYOMA VIRUS.

Dulbecco R, Johnson T
Salk Inst. Biol. Stud., San Diego, Calif.
Virology; 42(2):368-374 1970

The effect of large doses (100 and 200 U/ml) of purified interferon (produced in L-929 cells with Newcastle Disease virus) on the induction of cellular and viral DNA synthesis by polyoma virus or its Ts-a mutant in 3T3 cells was studied. Interferon (100 U/ml) inhibited 3H-thymidine incorporation into both viral (64-73% inhibition) and cellular (40-75%) DNA in polyoma-infected cells to a similar extent; as it also inhibited label incorporation into cellular (56-62%) DNA in Ts-a-infected cells. 3H-Thymidine incorporation was also slightly inhibited by interferon in uninfected cells (13-15%) but this was probably caused by the high doses of interferon used and by its high degree of purity.

C.
Effects of Interferons on Viral Nucleic Acid Translation

25. INTERFERON ACTION-SEQUENCE SPECIFICITY OF THE PPP(A2'P)NA-DEPENDENT RIBONUCLEASE.

Wreschner DH, McCauley JW, Skehel JJ, Kerr IM
Dept. Microbiology, Tel Aviv Univ., Ramat Aviv, Israel
Nature (Lond); 289(5796):414-417 1981

The sequence specificities of the 2-5A-dependent ribonucleases in extracts of rabbit reticulocytes, mouse ascites tumor cells, and human lymphoblastoid cells were investigated in conditions of partial digestion using terminally-labeled RNA substrates. Virus ribonucleic acids were labeled at their 3'-termini and purified by polyacrylamide gel electrophoresis. The products of 2-5A-activated ribonuclease activity and those obtained by limited chemical degradation were analyzed by comparative electrophoresis. In most cases, cleavages were observed at UN sequences where UA (U, uridine; A, adenine) and UU were preferred. When the products obtained using 5'-terminally labeled influenza virus RNA 8 were examined, all of the products obtained from the reticulocyte lysate were phosphorylated at their 3'-termini and their 3'-terminal sequences were UpNp. It was emphasized that, although the 2-5A-dependent nucleases from different sources showed similar specificities, they may not be identical. Cleavage was not obtained at all UA and UU sequences, perhaps because the specificity was also influenced by the secondary structure of the substrate. (24 Refs)

26. RADIOIMMUNE, RADIOBINDING AND HPLC ANALYSIS OF 2-5A AND RELATED OLIGONUCLEOTIDES FROM INTACT CELLS.

Knight M, Cayley PJ, Silverman RH, Wreschner DH, Gilbert CS, Brown RE, Kerr IM
Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England
Nature (Lond); 288(5787):139-192 1980

High performance liquid chromatography (HPLC) and radioimmune (RI) and radiobinding (RB) techniques were used to detect 2-5A synthetase (2-5A) and its nonphosphorylated 'core' in crude extracts from interferon (IF)-treated EMC virus-infected mouse L-cells. The RI assay was a sensitive method for the detection of core but could not be used to measure core in the presence of high concentrations of 2-5A without prior fractionation. The RB assay showed even greater specificity for 2-5A. Both RI and RB assays showed relatively high concentrations of 2-5A + core in a trichloroacetic acid-soluble extract from IF-treated, EMC virus-infected L cells and much lower concentrations in corresponding extracts from control cells, uninfected cells treated with IF, and virus-infected cells not treated with IF. The results of HPLC confirmed that most of the material detected by RI and RB was 2-5A. RB and RI detected the trimer and tetramer components of 2-5A at similar concentrations, but the RI assay also indicated the presence of preexisting core in amounts similar to those observed for the phosphorylated components. The RI assay also detected dimer and a cross-reacting material, which was probably adenosine. The data suggest the possible involvement of the 2-5A system in the cell growth inhibitory activity of IF. (22 Refs)

27. ANTIVIRAL RESPONSE AND INDUCTION OF SPECIFIC PROTEINS IN CELLS TREATED WITH IMMUNE T (TYPE II) INTERFERON ANALOGOUS TO THAT FROM VIRAL INTERFERON (TYPE I)-TREATED CELLS.

Hovanessian AG, Meurs E, Aujean O, Vaquero C, Stefanos S, Falcoff E
Unite d'Oncologie Virale, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris Cedex 15, France
Virology; 104(1):195-204 1980

Treatment of mouse L929 cells with immune T (Type II) interferon resulted in the induction of two double-stranded (ds) RNA-dependent enzymes which have been described previously in viral (Type I) interferon-treated cells: pppA(2'p5'A)n synthetase and protein kinase(s). The induction of these enzymes by T interferon was blocked by anti-T but not by antiviral interferon serum. The kinetics of the development of the antiviral state along with a comparison of the levels of pppA(2'p5'A)n synthetase and protein kinase in T and viral interferon-treated cells were investigated. In addition, [35S]methionine-labeled extracts from control, T, and viral interferon-treated cells were analyzed by sodium dodecyl sulfate - polyacrylamide gel electrophoresis and two-dimensional gel electrophoresis. Extracts from cells treated with either type of interferon were found to contain several identical proteins, of estimated mol wt 60,000, 80,000 and 120,000, which were absent or found at much lower levels in preparations from control cells. The newly synthesized proteins can be partially purified by chromatography on columns of poly(I)-poly(C)-Sepharose, thus providing a convenient method for their further characterization. These results show that treatment of cells with T interferon results in the induction of intracellular events identical to those observed in viral interferon-treated cells. (Author abstract) (47 Refs)

28. INTERFERON ENHANCES 2-5A SYNTHETASE IN EMBRYONAL CARCINOMA CELLS.

Wood JN, Hovanessian AG
Viral Oncology Unit, Institut Pasteur, Paris 15, France
Nature (Lond); 282(5734):74-76 1979

The activities of two double-stranded RNA-dependent enzymes, 2-5A synthetase and a protein kinase, were measured to determine the responsiveness of embryonal carcinoma (EC) stem cells to interferon. The enzyme 2-5A synthetase forms oligonucleotides of the series ppA(2'p5'A)n which potentially inhibit protein synthesis in vitro and in vivo. The following cell lines were studied: mouse teratocarcinoma cell lines PCC3/A/1 and PCC4AzaR1; PCC3/A/1-D-1M, a cloned differentiated derivative of PCC3/A/1; and mouse L929 cells, which respond to interferon by establishing an antiviral state and were used as differentiated controls. Enzyme activities were assayed after partial purification on columns of polyinosine/polycytosine-Sepharose. L929 cells and PCC3/A/1-D-1M cells showed enhanced phosphorylation by kinase after treatment with interferon, while PCC3/A/1 and PCC4AzaR1 cells did not. In contrast to the differences in kinase induction, both EC cells and differentiated cells showed similarly enhanced levels of 2-5A synthetase activity after interferon treatment. Antiviral and anticellular effects of interferon were assayed by the resistance of cells to vesicular stomatitis virus (VSV) infection and by inhibition of cell multiplication. No resistance to VSV was induced in EC cells by interferon, whereas L929 and 3/A/1-D-1M cells showed complete resistance to viral infection. Similarly, the interferon-mediated inhibition of cell growth in L929 and 3/A/1-D-1M cells was not observed in EC cells, even at high concentrations of interferon. The results demonstrate the lack of correlation between the induction of 2-5A synthetase and the establishment of an antiviral state or anticellular effects in undifferentiated EC cells. (30 Refs)

29. CELL-FREE PROTEIN SYNTHESIS AND INTERFERON ACTION: PROTEIN KINASE(S) AND AN OLIGONUCLEOTIDE EFFECTOR, PPPA2'P5'A2'P5'A.

Kerr IM, Williams BR, Hovanessian AG, Brown RE, Martin EM, Gilbert CS, Birdsall NJ
Natl. Inst. Medical Res., Mill Hill, London NN7 1AA, England
Haematol Blood Transfus; 23:291-294 1979

When an extract from interferon-treated cells is incubated with double-stranded RNA (dsRNA) and ATP, a protein kinase(s) which is thought to phosphorylate one of the initiation factors (eIF-2) involved in protein synthesis is activated. When interferon-treated cell extracts are incubated with dsRNA and ATP, an enzyme (2-5A synthetase) responsible for the synthesis of the unusual oligonucleotide pppA2'p5'A2'p5'A (2-5A) is also activated. Both the 2-5A synthetase and the kinase bind to a column of dsRNA, itself bound to sepharose. Various studies have revealed that 2-5A activates a nuclease. The 2-5A, the nuclease and the inhibition of protein synthesis are all unstable. On addition of exogenous 2-5A to cell-free systems, a nuclease is activated and protein synthesis is inhibited. Meanwhile, the 2-5A is degraded, nuclease activity diminishes, and protein synthesis resumes. It is clear that cells have a mechanism(s) for coping with 2-5A and the components interacting with 2-5A appear subject to cyclic activation and deactivation; 2-5A is active in both cell-free systems and in intact cells. That the 2-5A system may be involved in the regulation of normal cell growth or development is discussed. (15 Refs)

30. NATURAL OCCURRENCE OF 2-5A IN INTERFERON-TREATED EMC VIRUS-INFECTED L CELLS.

Williams BR, Golgher RR, Brown RE, Gilbert CS, Kerr IM
Natl. Inst. Medical Res., Mill Hill, London, Eng
Nature (Lond); 282(5739):582-586 1979

Until now the interferon-mediated 2'-5' adenine oligonucleotide inhibitors (2-5A) of cell-free protein synthesis have not been detected in intact cells. Here we report their natural occurrence in interferon-treated, encephalomyocarditis (EMC) virus-infected mouse L cells in amounts consistent with the idea that they play a part in the inhibition of virus growth. (Author abstract) (30 Refs)

31. CELL-FREE PROTEIN SYNTHESIS AND INTERFERON ACTION: PROTEIN KINASES AND AN OLIGONUCLEOTIDE EFFECTOR, PPPA2'P5'A2'P5'A (MEETING ABSTRACT).

Kerr IM
Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England
Modern Trends in Human Leukemia III Proceedings of a Meeting held in Wilsede, W Germany, 19-23 June, 1978, Berlin, Springer, to be published, 1979

The interferons are glycoproteins which are produced in response to virus infection. On exposure to interferon animal cells develop an antiviral state in which the growth of a wide spectrum of viruses is inhibited. Protein synthesis in cell-free systems from interferon-treated cells shows an enhanced sensitivity to inhibition by double-stranded RNA. An oligonucleotide, a protein kinase(s) and a nuclease appear to be involved. The oligonucleotide has the structure pppA2'p5'A2'p5'A in which the 2'-5' linkage is unusual, not having been reported previously for biological material. Although enhanced by interferon, its synthesis does not appear to be restricted to interferon-treated cell material. It is also made in large amounts, for example, in extracts from rabbit reticulocytes. Thus, its activity at subnanomolar concentrations and possible correlation with protein kinases makes it tempting to speculate that it may be of wider significance in the control of cell growth or development. It is small enough for it and analogs to be amenable to chemical synthesis. The role of the oligonucleotide, the kinase and the nuclease in the inhibition of cell-free protein synthesis and the sequence of events which follows infection of the interferon-treated cell are currently under investigation. (no Refs)

32. DUAL ACTION OF DOUBLE-STRANDED RNA IN INHIBITING PROTEIN SYNTHESIS IN EXTRACTS OF INTERFERON-TREATED MOUSE L CELLS. TRANSLATION IS IMPAIRED AT THE LEVEL OF INITIATION AND BY MRNA DEGRADATION.

Lewis JA, Falcoff E, Falcoff R
Dept. Anatomy and Cell Biology, Downstate Medical Center, State Univ. New York, 450 Clarkson Ave., Brooklyn, NY, 11203
Eur J Biochem; 86(2):497-509 1978

We have investigated the mechanism by which double-stranded RNA (dsRNA) inhibits protein synthesis in cell-free extracts prepared from mouse L cells which had been pre-treated with purified interferon. Preincubation of such extracts for a determined period of time causes inactivation of transfer RNA (tRNA) species and hence an inhibition of protein synthesis with either Mengo RNA or polyuridylic, polycytidylic acid [poly(U,C)] as messenger RNA (mRNA). This inhibition can be overcome by addition of tRNA. We show that dsRNA inhibits the translation of Mengo RNA irrespective of the period of preincubation and that this inhibition is not overcome by tRNA. Translation of poly(U,C) is unaffected by dsRNA. Thus dsRNA does not act at the level of peptide chain elongation and does not cause inactivation of tRNA species, indicating that dsRNA inhibits protein synthesis in extracts of interferon-treated cells by a mechanism which is different from that responsible for the inhibition observed in the absence of dsRNA. The addition of dsRNA to extracts prepared from interferon-treated cells causes two modifications which are expected to inhibit protein synthesis. (a) An enhancement of the level of nuclease activity, causing Mengo [3H]RNA to be degraded more rapidly in interferon-treated cell extracts than control extracts, even when association of Mengo RNA with ribosomes is inhibited by the addition of pactamycin. (b) An impairment in the formation of methionyl-tRNA-40-S-ribosomal-subunit complexes. The reduced binding of methionyl-tRNA to 40-S subunits can be overcome by the addition of a crude initiation factor preparation suggesting that dsRNA causes inactivation of an endogenous initiation factor(s). In the early stages of translation of Mengo RNA (10-15 min) dsRNA causes a reduction in the incorporation of [35S]methionine into the N-terminal position of polypeptides suggesting that initiation of protein synthesis is impaired, presumably as a result of the block of methionyl-tRNA-40-S-subunit complex formation. At a later stage (30-45 min) Mengo RNA is almost completely destroyed under the normal conditions of protein synthesis. (Author abstract) (40 Refs)

33. INFLUENCE OF PREINCUBATION ON THE DEVELOPMENT OF THE INHIBITION OF PROTEIN SYNTHESIS IN EXTRACTS FROM INTERFERON-TREATED MOUSE L CELLS. ACTION ON TRNA.

Falcoff R, Falcoff E, Sanceau J, Lewis JA
Fondation Curie Inst. Radium, 26 rue d'Ulm, Paris 75005, France
Virology; 86(2):507-515 1978

Treatment of cells with interferon leads to an inhibition of cell-free protein synthesis in preincubated cell extracts. We show here that the observation of such a defect in the translation of both Mengo virus RNA and poly(uridine,cystine) [poly(U,C)] depends critically upon the length of preincubation period. Control and interferon-treated cell extracts (Cont S-10, Int S-10) preincubated for up to 60 min have identical protein synthetic activity when assayed with either Mengo virus RNA or poly(U,C). Although preincubation of Cont S-10 for more than 60 min leads to a gradual reduction in the protein synthetic capacity of the extract, the activity of Int S-10 declines much more rapidly, and after 60 to 120 min of preincubation the translational activity of Int S-10 is markedly inhibited (80-90%) compared to Cont S-10. In extracts preincubated for times sufficient to allow the development of this impaired protein synthesis, addition of both total transfer (t)RNA and a purified leucine tRNA restores synthesis by Int S-10 to almost the same level as the corresponding controls. Addition of total tRNA, but not leucine tRNA, also overcomes the loss of activity observed in Cont S-10 extracts which have been preincubated for more than 60 min. Addition of leucine tRNA to Int S-10 during the preincubation step strongly reduces the ability of the tRNA to restore protein synthesis. Int S-10 programmed with Mengo virus RNA synthesized the same polypeptides as Cont S-10 when the preincubation period was 60 min or less. Although preincubation of Cont S-10 for more than 60 min led to a decline in their activity, the pattern of polypeptides synthesized was not affected. However, preincubation of Int S-10 for more than 60 min caused a decrease in the size of polypeptides as well as a reduction in their amount. Only peptides, of mol wt 7,000 to 26,000, were detected in such extracts. Our results indicate that preincubation of cell-free extracts leads to a decline in the capacity to utilize

tRNA and that pretreatment of the cells with interferon strongly enhances this effect, at least with respect to leucine tRNA. The inability of extracts prepared from interferon-treated cells to utilize endogenous tRNA after prolonged preincubation (60-120 min) is most probably due to inactivation of the tRNA. (Author abstract) (24 Refs)

34. THE USE OF A COMPLEMENTARY DNA PROBE TO DETECT ACCUMULATION OF MENGO RNA IN INFECTED CELLS PRETREATED WITH INTERFERON.

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J Steroid Biochem; 7(11/12):189-195 1977

Complementary DNA from Mengo virus RNA was synthesized and used as a probe to measure the synthesis and accumulation of viral RNA in Mengo infected cultures of mouse L cells (clone CCL1) that were either treated or not treated with interferon (200 units/ml added 40 hr prior to infection with 50 plaque forming units (pfu)/cell). One hr postinfection, when mature viruses could not be detected, progeny Mengo RNA formation had already started, with 200 molecules being accumulated in control cells and 60 in interferon-treated cells. Interferon pretreatment of the cells resulted in a 10-fold decrease in Mengo RNA accumulation 5 hr after infection. Although not completely abolished, virus production was also reduced in interferon-treated cells, being 0.13 pfu/cell at 5 hr and 4 pfu/cell at 7 hr. Thus, not only was RNA accumulation reduced in interferon-treated cells but some process subsequent to RNA synthesis also was apparently affected. (17 Refs)

35. INDUCTION OF 2',5'-OLIGOADENYLATE SYNTHETASE AND INTERFERON IN MOUSE TRIGEMINAL GANGLIA INFECTED WITH HERPES SIMPLEX.

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Infect Immun; 28(3):719-723 1980

The activity of 2',5'-oligoadenylate synthetase, which is induced by interferon action, was detected in mouse trigeminal ganglia infected with herpes simplex virus (HSV) type 1. When HSV was inoculated on the left cheek of mice, the virus began to appear in the ipsilateral trigeminal ganglia on day 2, reached its max accumulation on day 4, declined thereafter, and was no longer detected in the tissue homogenate after 11 days. After this short acute productive phase, the virus entered into the latent phase of infection. 2',5'-Oligoadenylate synthetase appeared in the trigeminal ganglia shortly after the beginning of virus multiplication; the synthetase activity began to rise on day 3, reached a max level on day 4, and then declined. Interferon activity (type I) also appeared in the infected ganglia, but diminished more rapidly than the synthetase. The antibody against HSV in the sera began to appear at the time when the virus and synthetase were declining. From these results it may be hypothesized, although not concluded, that in the acute productive phase of HSV infection in mouse trigeminal ganglia, virus multiplication is suppressed by interferon action, including 2',5'-oligoadenylate synthetase induction. (Author abstract) (21 Refs)

36. MECHANISM OF INTERFERON ACTION: SIMIAN VIRUS 40-SPECIFIC EARLY POLYPEPTIDES SYNTHESIZED IN UNTREATED AND INTERFERON-TREATED MONKEY KIDNEY CELLS.

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Proc Natl Acad Sci USA; 77(5):2419-2423 1980

The effect of interferon treatment on proteins synthesized in simian virus 40 (SV40)-infected cells in the presence of cytosine arabinoside was investigated. The following results were obtained: (i) In addition to previously described large tumor (T) antigen (94 kilodaltons (kDal)) and small tumor (t) antigen (19 kDal), a 62-kDal polypeptide was immunoprecipitated by SV40 anti-T antiserum from extracts of infected CV-1 and BSC-1 monkey kidney cells and transformed SV3T3 mouse cells. The 94-, 62-, and 19-kDal polypeptides were not precipitated with normal serum from extracts of infected cells, and they were not present in extracts of uninfected cells. (ii) The de novo synthesis of the 94-, 62-, and 19-kDal tumor antigens was inhibited in CV-1 and BSC-1 cells treated with interferon before infection; total cellular protein synthesis was not significantly affected by interferon treatment. The relative interferon sensitivity of the three polypeptides in lytically infected monkey cells was comparable; by contrast, interferon did not affect their synthesis in transformed mouse cells. (iii) The 62-kDal polypeptide was detected in monkey cells infected with the following strains of SV40: tsA30 at both 33 C and 41 C; wt 708, the parent of tsA30; dl 884, and wt 830, the parent of dl 884. The amount of the 62-kDal species relative to T antigen was significantly greater in tsA30-infected cells as compared to cells infected with other SV40 strains. (iv) T, t, and 62-kDal polypeptides were readily labeled with [35S]-methionine during a 10-min pulse; in a subsequent chase, the 35S-labeled 94-kDal T antigen was apparently converted to 89-and 84-kDal polypeptides but not to either the 62-kDal polypeptide species or t antigen. (v) Partial peptide maps suggest that the 62-kDal polypeptide and T antigen are closely related. (vi) In addition to the above described 62-kDal polypeptide, a 54-kDal polypeptide was also detected. However, the 54-kDal species appears to be of cellular origin because it was immunoprecipitated with both normal and anti-T antiserum from uninfected and lytically infected cells and from virally transformed cells. (Author abstract) (43 Refs)

37. MECHANISM OF INTERFERON ACTION. INTERFERON-MEDIATED INHIBITION OF REOVIRUS MRNA TRANSLATION IN THE ABSENCE OF DETECTABLE MRNA DEGRADATION BUT IN THE PRESENCE OF PROTEIN PHOSPHORYLATION.

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Virology; 107(2):461-475 1980

The effect of treating mouse fibroblast L cells with interferon on the ability of nonpreincubated and micrococcal nuclease-treated extracts prepared from them to catalyze reovirus messenger RNA translation, protein phosphorylation, and messenger RNA degradation was investigated both in the presence and the absence of exogenously added double-stranded RNA (dsRNA) and transfer RNA (tRNA). The following results were obtained: (1) Phosphorylation of ribosome-associated protein P1 and protein synthesis initiation factor eIF-2alpha was enhanced in both nonpreincubated and micrococcal nuclease-treated extracts prepared from interferon-treated cells. The enhancement in phosphorylation

was dependent upon the presence of reovirus dsRNA, although the apparent dsRNA requirement could also be fulfilled by reovirus mRNA at concentrations of mRNA typical of those used in cell-free protein synthesizing systems. (2) By contrast, the degradation of reovirus [3H]mRNA was enhanced in extracts prepared from interferon-treated cells when nonpreincubated, but not when micrococcal nuclease-treated and supplemented with ethyleneglycol-bis(beta-aminoethyl ether)-N,N'-tetraacetic acid (EGTA) and 2'-deoxythymidine-3',5'-diphosphate (pTp). The enhancement in degradation observed in nonpreincubated extracts lacking EGTA and pTp was dependent upon the presence of dsRNA and the absence of tRNA; enhanced dsRNA-dependent degradation was not detectable in the presence of tRNA. The limited degradation of reovirus [3H]mRNA, in both the presence and the absence of dsRNA and tRNA, was comparable in EGTA- and pTp-supplemented micrococcal nuclease-treated extracts prepared from either interferon-treated or untreated cells. The addition of 2',5'-oligoadenylate enhanced degradation in nonpreincubated extracts. (3) Reovirus mRNA was translated poorly by interferon-treated as compared to untreated systems in both the nonpreincubated and the micrococcal nuclease-treated extracts in the absence of reovirus dsRNA. The presence of dsRNA further decreased the translation by interferon-treated systems. The efficiency of endogenous cellular mRNA translation by untreated as compared to interferon-treated systems was comparable in nonpreincubated extracts, both in the presence and absence of dsRNA. The addition of mouse ascites tRNA stimulated translation in both untreated and interferon-treated systems, both in nonpreincubated and micrococcal nuclease-treated extracts. These results suggest that the translation of reovirus mRNA in interferon-treated systems is inhibited both in the presence and absence of interferon-mediated mRNA degradation, and that protein phosphorylation may play a primary role in regulating translation in interferon-treated cells. (Author abstract) (53 Refs)

38. MECHANISM OF INTERFERON ACTION. KINETICS OF INTERFERON ACTION IN MOUSE L929 CELLS: PHOSPHORYLATION OF PROTEIN SYNTHESIS INITIATION FACTOR EIF-2 AND RIBOSOME-ASSOCIATED PROTEIN P.

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Virology; 93(1):281-285 1979

Ribosomal salt-wash fractions prepared from interferon-treated mouse L929 fibroblast cells catalyze the phosphorylation of the small subunit (a) of protein synthesis initiation factor eIF. The effect of the duration of interferon treatment of L929 cells on the ability of the ribosomal salt-wash fractions to catalyze the phosphorylation of the 38,000-dalton alpha eIF-2 subunit, as well as the phosphorylation of the ribosome-associated protein P1, correlates with the appearance of the ribosome-associated inhibitor of translation. Protein P1 is also detectable in interferon-treated human amnion U cells. However, the apparent mol wt of P1 from interferon-treated U cells (approx 69,000 daltons) is slightly greater than that of P1 from interferon-treated L929 cells (approx 67,000 daltons). (Author abstract) (30 Refs)

39. MECHANISM OF INTERFERON ACTION. KINETICS OF INTERFERON ACTION IN MOUSE L929 CELLS: TRANSLATION INHIBITION, PROTEIN PHOSPHORYLATION, AND MESSENGER RNA METHYLATION AND DEGRADATION.

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Virology; 83(1):56-71 1977

The effect of the duration of interferon treatment of mouse L929 fibroblasts on the expression of ribosome-associated and cell-sap-localized translation inhibition, protein phosphorylation, and messenger RNA (mRNA) methylation and degradation was investigated. The following results were obtained: (1) Ribosomal salt-wash fraction (Ribo-swf), prepared from L929 cells treated for 12 or 18 hr, significantly inhibited the translation of methylated reovirus mRNA catalyzed by the cell-free system prepared from untreated ascites tumor cells. The translation of reovirus mRNA was slightly stimulated by the Ribo-swf prepared from untreated cells and cells treated for 2 hr and was slightly inhibited by the Ribo-swf from cells treated for 6 hr. (2) Cell-sap fractions prepared from untreated cells and from cells treated for 2 or 6 hr did not appreciably affect the translation of reovirus mRNA in the absence of double-stranded RNA (dsRNA); cell-sap fractions prepared from cells treated for 12 or 18 hr were slightly inhibitory. (3) Neither reovirus genome dsRNA nor polyriboinosinic acid-polyribocytidylic acid inhibited the translation of reovirus mRNA by the untreated ascites system. The inhibitory activity Ribo-swf from interferon-treated cells was dsRNA independent, whereas dsRNA enhanced the inhibitory activity of cell-sap fractions from interferon-treated cells. (4) Interferon significantly enhanced a cell-sap-independent phosphorylation of at least three proteins present in the Ribo-swf. Phosphorylation of a 50,000-dalton component was maximally enhanced after 12 hr of interferon treatment and was increased by dsRNA; phosphorylation of 30,000-and less than 20,000-dalton components was enhanced earlier and was dsRNA independent. (5) An increase in the nuclease-mediated degradation of [H 3]-uridine labeled methylated reovirus mRNA catalyzed by Ribo-swf was detectable after 6 hr of interferon treatment and was maximally enhanced after 12 hr of interferon treatment to about three-fold the level of the untreated Ribo-swf. The degradation was not enhanced by dsRNA. The levels of reovirus mRNA degradation catalyzed by cell-sap fractions from untreated cells and from cells treated with interferon for 2 to 18 hr were comparable. (6) No significant difference was observed in the ability of cell-sap fractions from untreated cells or from cells treated with interferon for 2 to 18 hr to catalyze the methylation of unmethylated reovirus mRNA. In addition, none of the Ribo-swf significantly inhibited reovirus mRNA methylation catalyzed by untreated ascites cell-free extracts. These results suggest that interferon treatment may mediate multiple biochemical changes in murine cells, including the specific phosphorylation of protein(s) associated with ribosomes that possess *interferon-mediated inhibitor(s) of viral mRNA translation.* (Author abstract) (47 Refs)

40. MECHANISM OF INTERFERON ACTION: STUDIES ON THE MECHANISM OF INTERFERON-MEDIATED INHIBITION OF REOVIRUS MESSENGER RNA TRANSLATION IN CELL-FREE PROTEIN SYNTHESIS SYSTEMS FROM MOUSE ASCITES TUMOR CELLS.

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Virology; 75(1):166-176 1976

Ascites cells in the ascitic form were treated with partially purified interferon by injection of 1 x 10(4) units into the peritoneal cavity of female albino mice 6 days after cell passage; a second dose was given about 8 hr later and cells were collected 18 hr after. Cell-free extracts were prepared from untreated and interferon-treated cells, and the following were studied in vitro: rate of formation and yield of reovirus methionyl-X initiation dipeptides, overall translation of reovirus messenger RNA (mRNA), structural integrity of reovirus mRNA recovered from in vitro protein synthesis systems, and the effect of exogenously added transfer RNA (tRNA), S-adenosyl-L-methionine (SAM), and S-adenosyl-L-homocysteine (SAH) on the translation in vitro of reovirus mRNA. Extracts from interferon-treated cells catalyzed the formation of methionyl-X initiation dipeptides in response to reovirus mRNA at a rate and extent only slightly less than that of extracts from untreated cells. When the interferon-mediated inhibition of overall translation in vitro of reovirus mRNA was > 75%, formation of methionyl-X initiation dipeptides was inhibited much less, about 30%. Neither methionyl-X initiation dipeptide formation nor overall translation of reovirus mRNA was significantly affected by adding SAM or SAH to systems of treated or untreated cells. The translation of reovirus mRNA synthesized in the presence of SAM was slightly more efficient than that of either reovirus mRNA synthesized in the presence of SAH or reovirus mRNA synthesized in the absence of both SAM and SAH when catalyzed by untreated-cell extracts. Extracts from treated cells translated all three types of reovirus mRNA very poorly in the standard protein synthesis system. Interferon-mediated inhibition of viral mRNA translation in interferon-treated systems was partially reversed by adding mouse ascites cell tRNA; tRNA from yeast, rat liver, Escherichia coli, and Streptococcus faecalis did not stimulate reovirus mRNA translation in the treated system. Labeled reovirus mRNA which was recovered from treated systems after 15-min incubations was similar to that from untreated systems when analyzed by polyacrylamide-agarose-urea gel electrophoresis. These results indicate that the interferon-mediated inhibition of viral mRNA translation is exerted at a step of polypeptide chain biosynthesis which is subsequent to formation of the first peptide bond and which either directly or indirectly involves participation of tRNA. (36 refs)

41. SYNTHESIS OF TWO NON-PHOSPHORYLATED PROTEINS INDUCED IN MOUSE L-CELLS BY HOMOLOGOUS INTERFERON.

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Biochem Biophys Res Commun; 96(4):1592-1602 1980

Two proteins, P1 and P2, with mol wt of 43,000 and 40,800, respectively, and isoelectric points of pH 4.6 and pH 4.7, respectively, were detected in interferon (IF)-treated mouse L-929 cell extracts. In control cells not treated with IF, P1 was detectable only in small amounts and P2 was absent. When added at the same time as IF, actinomycin D (A-D) prevented the IF-induced antiviral state of L-929 cells and the appearance of protein kinase (PKase) and oligoadenylate synthetase (OASase) activities, suggesting that an early DNA transcription event is needed for the induction of these two enzymes. When A-D was added to cell extracts 4-6 hr after IF treatment, the antiviral action induced by IF was potentiated, and PKase and OASase activities were increased. The same evolution was observed in parallel for P1 and P2 synthesis. Double-labeled two-dimensional gel studies indicated that neither P1 nor P2 is phosphorylated. (29 Refs)

42. INTERFERON-INDUCED (2',5')OLIGOADENYLATE SYNTHETASE: ADSORPTION TO AND ASSAY ON ADENOSINE 2',5'-DIPHOSPHATE-SEPHAROSE.

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Biochemistry (Washington); 19(24):5580-5585 1980

We have developed a new assay method for 2',5'-oligoadenylate synthetase based on adsorption of crude cell extracts to ADP-Sepharose at 4 C. After binding the enzyme from cell lysates, the resin was washed and incubated at 30 C in the presence of ATP and double-stranded RNA (dsRNA). The 2',5'-ppp(Ap)nA[(2',5')oligo(A)] product was assayed by its ability to inhibit protein synthesis in a micrococcal nuclease pretreated mouse L cell extract programmed by encephalomyocarditis (EMC) viral RNA. By use of extracts from interferon-treated mouse L cells, the levels of (2',5')oligo(A) produced by this method were comparable to those obtained under identical conditions by using poly(inosinic acid)-poly(cytidylic acid) [(I)n-(C)n]-Sepharose and were higher than the amounts obtained in a direct soln assay. Preformed (2',5')oligo(A) was more stable under the conditions of the 2',5'-ADP-Sepharose binding assay than under the soln assay conditions. In addition, the synthetase was relatively stable when attached to the resin; substantial activity remained after 24 hr at 30 C. Synthesis of (2',5')oligo(A) was linear for approx 5 hr and was proportional to the amount of extract bound and to the concentration of ATP in the reaction incubation. The reaction was stimulated by Mg++ concentrations up to approx 10 mM and was independent of the K+ concentration at levels below 0.1 M. The amount of (2',5')oligo(A) produced depended on the amount of and the nature of the dsRNA present. Activating nucleic acids that varied in potencies over a 10,000-fold range could be distinguished. The convenience and range of this assay make it suitable for the assay of 2',5'-oligoadenylate synthetase in crude cell extracts when a direct soln assay does not provide high yields of (2',5')oligo(A) or when variation of the nature and/or concentration in the nucleic acid activator is desired. (Author abstract) (32 Refs)

43. A LARGE GLYCOPROTEIN OF MOLONEY LEUKEMIA VIRUS DERIVED FROM INTERFERON-TREATED CELLS.

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Biochem Biophys Res Commun; 77(1):392-398 1977

The glycoproteins (gp) of low infectivity Moloney leukemia virus produced in interferon-treated TB cells were studied. Two methods were used to label the viral glycoproteins: infected cells were incubated with H3-glucosamine and then purified; or purified virus was treated with sodium metaperiodate and then labeled with tritiated sodium borohydride. With both methods, a glycoprotein with a molecular wt of about 85,000 (gp85) was detected in the virus derived from

interferon-treated TB cells while only a trace amount of this glycoprotein was present in virus derived from control cells not treated with interferon. The excess gp85 in virus derived from interferon-treated cells may be uncleaved precursor to gp 69-71. (22 Refs)

44. NUCLEASE ACTIVATION BY DOUBLE-STRANDED RNA AND BY 2',5'-OLIGOADENYLATE IN EXTRACTS OF INTERFERON-TREATED CHICK CELLS.

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Virology; 93(2):348-356 1979

Cell-free extracts were prepared from primary chick embryo cells that had been pretreated overnight with chick interferon or with mock preparations of interferon. After the addition of double-stranded RNA (dsRNA) to these extracts, the synthesis of vesicular stomatitis virus (VSV) messenger (m)RNA and its corresponding proteins was measured under conditions of coupled transcription and translation directed by purified virus. The addition of dsRNA to extracts of mock interferon-treated cells did not affect VSV-directed transcription or translation. However, in extracts of interferon-treated cells, the rate of RNA accumulation was inhibited by about 50% and that of the viral proteins by about 95% relative to the rates in control extracts. Furthermore, no intact VSV mRNA was detectable among the transcription products made in extracts of interferon-treated cells under these conditions. These results contrasted with those obtained in the absence of dsRNA, where the interferon-mediated inhibition of protein synthesis was less extreme, and where both sets of transcription products were intact and fully functional. The differences could be ascribed, at least in part, to a dsRNA-mediated increase in the rate of mRNA degradation that occurred only in extracts of interferon-treated cells. Enhancement of mRNA breakdown was also observed when protein synthesis was inhibited by the addition of pppA2'p5'A2'p'A and higher oligomers (2',5'-oligoadenylate) to extracts of either interferon-treated or mock interferon-treated cells. (These novel oligonucleotides are synthesized in interferon-treated cell extracts by an enzyme that requires dsRNA for activation). Under a variety of conditions, enhanced mRNA degradation correlated with the inhibition of protein synthesis mediated by 2',5'-oligoadenylate but not by other inhibitors. Thus, the data suggest that the inhibition of protein synthesis by dsRNA in extracts of interferon-treated chick cells is due, at least in part, to mRNA breakdown catalyzed by a nuclease that is activated by 2',5'-oligoadenylate. (Author abstract) (46 Refs)

45. INDUCTION OF 2'5'-OLIGOADENYLATE SYNTHETASE ACTIVITY AND A NEW PROTEIN BY CHICK INTERFERON.

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Microbiology Section, Univ. Connecticut, Storrs, CT, 06268
Virology; 94(2):282-296 1979

Treatment of primary cultures of chick embryo cells with homologous interferon increased the activity of 2'5'-oligoadenylate synthetase in their cytoplasmic extracts. The kinetics of enhancement showed an initial lag of about 1 hr, followed by a 4- to 5-hr period during which the activity increased exponentially. Max levels were reached about 10 hr after interferon treatment. Neither an increase in enzyme activity, nor the establishment of a virus-resistant state was observed in cells treated with chick interferon in the presence of actinomycin D or p-fluorophenylalanine, or in cells treated with heterologous (mouse) interferon. Analysis of the proteins labeled by incorporation of [35S]methionine after interferon treatment revealed the appearance of a new polypeptide in the postribosomal supernatants of interferon-treated cells. Upon gel filtration this polypeptide coeluted with the peak of oligoadenylate synthetase activity, at 50,000-60,000 mol wt. It had an apparent mol wt of 56,000 when analyzed by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate. Like the 2'5'-oligoadenylate synthetase activity, the 56,000-dalton polypeptide bound to polyriboinosinic acid-polyribocytidylic acid covalently attached to agarose and could be partially purified in this manner. The appearance of the polypeptide was dependent on the concentration of interferon and the time of treatment employed and was blocked by the presence of actinomycin D. Pulse-labeling studies showed that its rate of synthesis increased sharply about 2 hr after interferon treatment but decreased again about 8 hr later despite the continued presence of interferon in the medium. The possibility that the 56,000-dalton polypeptide is the oligoadenylate synthetase enzyme is being studied. These data suggest that the enzyme and the polypeptide are each the product of a gene whose function is controlled by interferon treatment. (46 Refs)

46. OLIGONUCLEOTIDE INHIBITOR OF PROTEIN SYNTHESIS MADE IN EXTRACTS OF INTERFERON-TREATED CHICK EMBRYO CELLS: COMPARISON WITH THE MOUSE LOW MOLECULAR WEIGHT INHIBITOR.

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Proc Natl Acad Sci USA; 75(3):1167-1171 1978

Cytoplasmic extracts of interferon (ITF)-treated primary chick embryo cells contain an enzyme activity that synthesized an inhibitor (INH) of chick cell-free protein synthesis. The same activity was detected in extracts of cells treated with mock preparations of ITF, but at less than 0.3% of the level found in ITF-treated cell extracts. The enzyme was activated by double-stranded RNA and could be isolated by binding to columns of poly(inosine)-poly(cytosine)-agarose. In the column-bound state, the enzyme was treated with ATP to synthesize the INH, which could then be continuously eluted from the column. The INH was purified and its structure and function were compared with those of the low mol wt INH of protein synthesis made by an enzyme from ITF-treated mouse L cells. The avian and mammalian INH comigrated on this layer of polyethyleneimine-cellulose during chromatography in three different solvent systems, and they coeluted as a series of peaks from columns of diethylaminoethyl cellulose during sodium chloride gradient elution. Digestion with bacterial alkaline phosphatase or snake venom phosphodiesterase yielded products that similarly comigrated. Both INHs inhibited protein synthesis in extracts of mammalian and avian cells, producing 50% inhibition at about 0.3 nanoM (AMP equivalents). We conclude that the chick cell-derived oligonucleotide INH has a structure that is closely related or identical to that of the INH made in the mouse system, and that both preparations inhibit cell-free protein synthesis in a non-species-specific manner. (Author abstract) (27 Refs)

47. ROLE OF 2',5'-OLIGO(ADENYLIC ACID) POLYMERASE IN THE DEGRADATION OF RIBONUCLEIC ACID LINKED TO DOUBLE-STRANDED RIBONUCLEIC ACID BY EXTRACTS OF INTERFERON-TREATED CELLS.

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Biochemistry (Washington); 19(24):5574-5579 1980

RNA covalently linked to double-stranded RNA (dsRNA) is preferentially degraded in extracts of interferon-treated HeLa cells. The size of the dsRNA required for this preferential degradation has been determined by annealing poly(I) of known length to the poly(C) tract of encephalomyocarditis virus (EMCV) RNA or by annealing poly(U) to poly(A) of known length of vesicular stomatitis virus mRNA. The dsRNA must be longer than about 60 base pairs to observe the preferential degradation of RNA. Moreover, triple-stranded regions that do not activate synthesis of 2',5'-oligo(A) and ethidium bromide, which intercalates in dsRNA and blocks 2',5'-oligo(A) polymerase activation, prevent this degradation. Ethidium also blocks the degradation of the replicative intermediate of EMCV by extracts of interferon-treated cells. These experiments indicate that synthesis of 2',5'-oligo(A) is required for the degradation of RNA linked to dsRNA. The 2',5'-oligo(A)-dependent endonuclease does not cleave single- or double-stranded DNA, nor does it cleave homopolyribonucleotides. The potential role of the 2',5'-oligo(A) polymerase/endonuclease system in the inhibition of viral RNA replication is discussed. (Author abstract) (27 Refs)

48. INCREASED LEVELS OF (2'-5')OLIGO(A) POLYMERASE ACTIVITY IN HUMAN LYMPHOBLASTOID CELLS TREATED WITH GLUCOCORTICOIDS.

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Proc Natl Acad Sci USA; 77(11,part2):6506-6510 1980

An enzymatic activity that synthesizes (2'-5')-oligo(A) from ATP is induced in animal cells treated with *interferon.* This activity, designated (2'-5')A polymerase, is also elevated in human lymphoblastoid Daudi and Raji cells treated with hydrocortisone. The polymerase activity increases significantly after 24 hr of treatment and declines when hydrocortisone is removed from the culture medium. The product of the enzyme prepared from hydrocortisone-treated cells is indistinguishable from (2'-5')oligo(A) synthesized with polymerase of interferon-treated cells either by an endonuclease activation assay or by chromatographic analysis. The increase in (2'-5')A polymerase is not mediated by secretion of interferon by hydrocortisone-treated cells; less than 1 unit of interferon per ml is present in the culture medium during treatment with this glucocorticoid hormone. Moreover, this increase is related to the concentration of hydrocortisone in the culture medium and is inhibited by the addition of cortexolone. This steroid interferes with the interaction between glucocorticoid hormones and their receptor. Cortexolone has no effect, however, on the induction of (2'-5')A polymerase by interferon. The synthetic glucocorticoid dexamethasone also increases the polymerase activity. Experiments with inhibitors show that such an increase requires RNA and protein synthesis. (Author abstract) (32 Refs)

49. MECHANISM FOR DISCRIMINATION BETWEEN VIRAL AND HOST MRNA IN INTERFERON-TREATED CELLS.

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Proc Natl Acad Sci USA; 76(6):2600-2604 1979

In extracts of interferon-treated HeLa cells, RNA covalently linked to double-stranded RNA (dsRNA) is preferentially degraded compared with messenger (m)RNA not linked to dsRNA. This was established by following the degradation of polyadenylic acid-containing mRNA annealed with polyuridylic acid, of polycytidylic acid-containing encephalomyocarditis virus RNA annealed with polyinosinic acid, and of the replicative intermediate of the virus isolated from infected cells. In extracts of interferon-treated cells, dsRNA promotes the synthesis of a series of oligonucleotides, designated (2'-5')oligoadenylic acid [oligo(A)], which in turn activate an endonuclease. Several lines of evidence suggest that the (2'-5')oligo(A) polymerase/endonuclease system is involved in the preferential degradation of mRNA linked to dsRNA. Conditions that prevent synthesis of (2'-5')oligo(A) prevent this preferential degradation, whereas addition of (2'-5')oligo(A) or conditions that favor its synthesis result in degradation of mRNA both linked and not linked to dsRNA. These results are best explained by a localized activation of the endonuclease near the dsRNA region of our model substrates. We propose that in infected cells activation of the endonuclease takes place near the replicative intermediates of RNA viruses. The replicative intermediates of encephalomyocarditis virus promote synthesis of (2'-5')oligo(A) in extracts of interferon-treated cells and are degraded to a 20 Svedberg 'core' resistant to digestion with ribonuclease A. This mechanism may be responsible for discrimination between viral and cellular mRNA in interferon-treated cells. (Author abstract) (25 Refs)

50. INHIBITION OF PROTEIN SYNTHESIS BY DOUBLE-STRANDED RNA IN RETICULOCYTE LYSATES: EVIDENCE FOR ACTIVATION OF AN ENDORIBONUCLEASE.

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Biochem Biophys Res Commun; 83(1):59-68 1978

The effects of double-stranded RNA (dsRNA) on reticulocyte cell-free protein synthesis were investigated and the activation of a nuclease was demonstrated. When reticulocyte lysates (RL) are incubated with dsRNA under conditions of protein synthesis, polysomes become disaggregated. In the presence of emetine (an inhibitor of chain elongation) dsRNA still caused limited but significant degradation of polysomes. This partial degradation may be caused by limited endonucleolytic cleavage of the messenger RNA (mRNA), amounting to one or two nicks per molecule. Exposure of radioactive Mengo virus RNA to dsRNA in RL at 30 C strongly enhanced the rate of degradation of the 34S (Svedberg) material to fragments sedimenting at less than 18S. However, dsRNA had no effect on the rate of appearance of acid soluble degradation products, indicating that it is an endonuclease rather than an exonuclease which has been activated. The results provide evidence that both endogenous globin RNA and exogenous Mengo virus RNA are physically degraded in RL upon incubation with dsRNA. It was also shown that incubation of lysates with dsRNA impaired the ability of mRNA to function as a template for protein synthesis. RNA from RL incubated for 60 min with 10(-8) g/ml dsRNA was only 12% as active as

RNA from control lysates in supporting protein synthesis. The dsRNA inactivation of mRNA was time-dependent. mRNA function was not impaired by heme-controlled repressor. The effects of dsRNA in RL and in extracts from interferon-treated mouse cells show many similarities. The nuclease activity in RL appears to be very similar to the interferon-dependent nuclease in the mouse cells. *Interferon*, therefore, may regulate protein synthesis by amplifying normal cellular control mechanisms. (31 Refs)

51. AN INTERFERON-INDUCED PHOSPHODIESTERASE DEGRADING (2'5')OLIGOISOADENYLATE AND THE C-C-A TERMINUS OF TRNA.

Schmidt A, Chernajovsky Y, Shulman L, Federman P, Berissi H, Revel M
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
Proc Natl Acad Sci USA; 76(10):4788-4792 1979

A phosphodiesterase characterized by a generally higher activity on 2'-5' than on 3'-5' phosphodiester bonds was isolated from mouse L cells treated with interferon. A similar enzyme was purified from mouse reticulocytes. The phosphodiesterase 2'-PDi splits the 2'-phosphate bond of pppA2'p5'A2'p5'A, the oligonucleotide activator of ribonuclease F. The level of phosphodiesterase 2'-PDi is increased by interferon treatment of L cells. The phosphodiesterase was also shown to degrade the cytidyl-cytidyl-adenyl terminus of transfer RNA (tRNA) and to reduce the amino acid acceptance of tRNA in cell free extracts, thereby causing a tRNA reversible inhibition of messenger RNA translation. (Author abstract) (35 Refs)

52. KINETICS OF THE INDUCTION OF THREE TRANSLATION-REGULATORY ENZYMES BY INTERFERON.

Kimchi A, Shulman L, Schmidt A, Chernajovsky Y, Fradin A, Revel M
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
Proc Natl Acad Sci USA; 76(7):3208-3212 1979

Three enzymes that cause inhibition of messenger RNA translation, eukaryotic initiation factor 2 protein kinase PK-i, oligoisoadenylate synthetase E, and phosphodiesterase 2'-PDi, have been recently isolated from interferon-treated cells. We show that the rise in these three enzyme activities may be used to study the response of uninfected cells to interferon. For each enzyme, a specific microassay that can be carried out on extracts from 2-5 x 10(4) monolayer cells from mouse, monkey, or man was developed. With these assays, the kinetics of induction of the three enzymes in mouse L cells are compared. The dose dependence for protein kinase PK-i induction is shown to be similar to that for the development of the antiviral state. Actinomycin D and anti-interferon serum block enzyme induction if added to the cells early after interferon treatment. The quantitative measurements of the intracellular level of these enzymes provide a new and convenient model to study the cell's response to interferon. (Author abstract) (34 Refs)

53. THE INTERFERON SYSTEM: STUDIES ON THE MOLECULAR MECHANISM OF INTERFERON ACTION.

Revel M, Kimchi A, Schmidt A, Shulman L, Zilberstein A
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
The Molecular Biology of Picornaviruses. Based on the Proceedings of the NATO International Advanced Study Institute on the Molecular Biology of Picornaviruses, held in Maratea (Gulf of Policastro), Italy, September 8-18, 1978. 371 pp., 1979.

Interferon-induced translational regulations are reviewed in terms of three pathways, which include increases in the enzymatic phosphorylation of endogenous proteins, oligo-isoadenylate synthesis and activation of nuclease F, and reduced ability of interferon-treated cell extracts to translate exogenous messenger (m)RNAs. It is suggested that the multiple effects by which interferon affects protein synthesis could each have a function in the cells. Transfer (t)RNA sensitive inhibition, seen in the absence of double-stranded (ds)RNA, may play its role mainly in the noninfected cell where dsRNA is very low or absent. After infection, in the case of many viruses, dsRNA is formed and accumulates. The protein kinase pathway is activated at low dsRNA concentrations, but at higher dsRNA levels it is switched off and the iso-adenylate-nuclease system may act. This multiphase antiviral state could insure that the interferon-induced control of gene expression is appropriate to the state of the cell. The three pathways of interferon-induced translation control share a common requirement for ATP and are regulated by antagonists. (35 Refs)

54. INTERFERON-INDUCED TRANSLATIONAL REGULATION.

Revel M
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
Tex Rep Biol Med; 35:212-220 1977

A review of the literature on the inhibition of viral replication by interferon is presented. In simian virus 40 (SV-40)-infected monkey cells, interferon treatment inhibited viral DNA synthesis but did not cause degradation of viral messenger (m)RNAs or affect host protein synthesis. However, the viral mRNAs would not associate with polyribosomes anymore. Whether interferon also directly affects viral RNA synthesis is not known at present. In cell-free systems, viral mRNAs were deficient in a capping structure after interferon treatment. However, these mRNAs were still able to direct synthesis of viral protein in a wheat germ cell-free system. Interferon has been found to induce translational inhibitory activity which affected viral and cellular mRNAs in most cases. There seems to be a strong correlation between induction of the antiviral state by interferon and the formation of translational inhibitory activity. The translational inhibitor(s) have not been identified yet. However, detailed kinetic studies have established that the inhibition affects both the elongation and initiation steps. Addition of double-stranded RNA, which induces interferon and is very toxic for cells treated with interferon, to cell-free systems is associated with the phosphorylation of several proteins. The phosphorylation of protein 67 appears to be a specific marker for the action of interferon. However, there is no conclusive evidence that protein phosphorylation is directly involved in the inhibition of mRNA translation. (67 Refs)

55. INHIBITION OF VIRAL PROTEIN SYNTHESIS IN MONKEY CELLS TREATED WITH INTERFERON LATE IN SIMIAN VIRUS 40 LYTIC CYCLE.

Yakobson E, Prives C, Hartman JR, Winocour E, Revel M
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
Cell (Camb); 12(1):73-81 1977

BSC-1 cultures were exposed to monkey interferon (100 U/ml) 18 hr before or 21 hr after infection with simian virus 40 (SV40, 25 plaque-forming U/cell). Pretreatment with interferon reduced the amount of early SV40 RNA, but treatment late in the lytic cycle did not inhibit viral RNA synthesis. Viral 19S and 16S RNA species were undiminished in quantity and poly(A) content. However, despite the apparent normalcy of viral RNA classes, there was a marked reduction in the synthesis of their protein products, (T antigen and capsid polypeptides). The association of viral RNA with heavy polyribosomes was strongly reduced. On the

other hand, there was no degradation of nonviral polyribosomes, and the synthesis of most cellular proteins continued. These experiments demonstrate that late in infection, interferon inhibits viral messenger RNA translation. (39 Refs)

56. INTERFERON-INDUCED PROTEINS IN HUMAN FIBROBLASTS AND DEVELOPMENT OF THE ANTIVIRAL STATE.

Rubin BY, Gupta SL
Interferon Lab., Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Virol; 34(2):446-454 1980

Treatment of human fibroblasts with interferon induces the synthesis of several proteins, as detected by incorporation of [35S]methionine followed by analysis of cell extracts by polyacrylamide gel electrophoresis. The induction of these proteins had features in common with the development of the antiviral effect of interferon, such as (i) sensitivity to actinomycin D and cycloheximide when these compounds were added together with interferon, (ii) insensitivity to actinomycin D if the actinomycin D was added 2 hr after the addition of interferon, (iii) similar dependence on interferon concentration, and (iv) species specificity for interferon. When interferon treatment was given in the presence of cycloheximide and actinomycin D was added before the removal of cycloheximide, all four proteins were induced, thus suggesting that their inductions are coordinated. Labeling for 2-hr periods at varying time intervals after the addition of interferon revealed that the synthesis of these proteins was induced within a few hr, peaked at different time intervals, and was soon followed by a marked decline, suggesting that the messenger RNA's for these proteins have short half-lives. Moreover, this decline occurred despite the fact that the cells were continuously exposed to interferon, and there was no measurable loss of interferon activity in the medium. This suggests that the induction of these proteins is transient and is apparently subject to further control. (Author abstract) (36 Refs)

57. SPECIFIC PROTEIN PHOSPHORYLATION IN INTERFERON-TREATED UNINFECTED AND VIRUS-INFECTED MOUSE L929 CELLS: ENHANCEMENT BY DOUBLE-STRANDED RNA.

Gupta SL
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J Virol; 29(1):301-311 1979

The enhanced phosphorylation of specific protein(s) observed in extracts from interferon-treated cells (in the presence of ATP and double-stranded [ds] RNA) was also seen in intact mouse L929 cells upon treatment with dsRNA, polyriboinosinic polyribocytidylic acid [poly(rI rC)] or reovirus dsRNA, using 32P as radiolabel. Labeling of a 65,000-dalton protein(s) with 32P was greatly increased in interferon-treated cells in the presence of added dsRNA, suggesting that the expression in vivo of the kinase activity involved is regulated by dsRNA. This was used as a test system to investigate whether the activity of interferon-induced enzyme(s) is stimulated following virus infection, possibly owing to the accumulation of dsRNA. No obvious increase in 32P-labeling of 65,000-dalton protein(s) was observed upon infection of interferon-treated cells with mengovirus or vesicular stomatitis virus. A basal level of 32P-labeling of the 65,000-dalton protein(s) was detected in interferon-treated cells in the absence of added dsRNA, indicating a basal level of expression of the kinase activity involved. The possible implications of these results are discussed. (Author abstract) (42 Refs)

58. INTERFERON, DOUBLE-STRANDED RNA, AND RNA DEGRADATION: ACTIVATION OF AN ENDONUCLEASE BY (2'-5')AN.

Slattery E, Ghosh N, Samanta H, Lengyel P
Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, CT, 06520
Proc Natl Acad Sci USA; 76(10):4778-4782 1979

Among the mediators of interferon action is one enzyme that is activated by double-stranded RNA to convert ATP to (2'-5')An and a second enzyme, an endonuclease, that is activated by (2'-5')An to cleave single-stranded RNA. The binding of (2'-5')An to the endonuclease (partially purified from mouse Ehrlich ascites tumor cells) is revealed by its retention on nitrocellulose filters. This can serve as the basis for an assay of the enzyme. Activation of the enzyme is reversible and is lost upon removal of (2'-5')An: gel filtration of activated endonuclease on Sephacryl S-200 results in an inactive enzyme. The enzyme can be activated again, however, by addition of (2'-5')An. The elution vol of the nonactivated endonuclease from Sephadex G-200 indicates that its mol wt is 185,000, unusually large for a nuclease. The elution vol of the maximally activated endonuclease from Sephadex G-200 equilibrated with (2'-5')An is not detectably different from that of enzyme that had not been previously activated that was passed through Sephadex G-200 not equilibrated with (2'-5')An. This indicates that the activation does not result in a large change in the size or conformation of the enzyme. (Author abstract) (27 Refs)

59. MESSENGER RNA METHYLATION, TRANSLATION AND DEGRADATION IN EXTRACTS OF INTERFERON-TREATED CELLS.

Sen GC, Desrosiers R, Ratner L, Shaila S, Brown GE, Lebleu B, Slattery E, Kawakita M, Cabrer B, Taira H, Lengyel P
Dept. Molecular Biophysics, Yale Univ., New Haven, CT, 06520
Tex Rep Biol Med; 35:221-229 1977

Extracts from interferon-treated, not virus infected Ehrlich ascites tumor (EAT) cells differ in several biochemical characteristics from extracts of untreated cells. Some of these differences are manifested only if the extracts are supplemented with double-stranded (ds) RNA and ATP. Thus, in the extracts from interferon-treated cells these supplements activate a protein kinase and an endonuclease activity as well as an inhibitor of the translation of messenger(m) RNA. The effect of the same supplements in extracts of untreated cells is much less pronounced. Other differences between the two types of extracts do not seem to depend on the addition of ds RNA and ATP. These include an impairment of mRNA cap methylation and an inhibition of peptide chain elongation that can be overcome by the addition to transfer RNA. The treatment of human (HeLa S3) cells with human interferon is manifested in the cell extract similarly to the treatment of EAT cells with mouse interferon. Studies are underway to isolate and characterize the ds RNA activated enzymes and the inhibitors and to establish how the presence of these in extracts from interferon-treated cells can account for the impairment of virus replication by interferon. (Author abstract) (27 Refs)

60. INTERFERON, DOUBLE-STRANDED RNA AND RNA DEGRADATION.

Ratner L, Sen G, Brown GE, Lebleu B, Kawakita M, Cabrer B, Slattery E, Lengyel P
Dept. Molecular Biophysics and Biochemistry, Yale Univ. New Haven, CT
Eur J Biochem; 79(2):565-577 1977

Extracts from interferon-treated Ehrlich ascites tumor cells differ in various biochemical characteristics from extracts

from control cells. Thus, as reported earlier, double-stranded RNA (dsRNA) promotes the phosphorylation by ATP of at least two proteins in extracts from interferon-treated cells, but not, or to only a lesser extent, in extracts from control cells. Moreover reovirus mRNAs are degraded faster in reaction mixtures containing extracts from interferon-treated cells than in those containing extracts from control cells but only if the reaction mixtures are supplemented with dsRNA and ATP. The faster RNA degradation in extracts from interferon-treated cells is due to enhanced endonuclease action. We designated the agent(s) catalyzing this as endonuclease(int). There is some enhancement of nuclease activity by dsRNA and ATP also in extracts from control cells. The extent of this enhancement is, however, much smaller than in extracts from interferon-treated cells. We report now that the promotion of mRNA cleavage in extracts from interferon-treated cells by dsRNA and ATP is apparently not a consequence of a possible impairment in the attachment of the mRNA to ribosomes since (a) the protein synthesis inhibitors (sparsomycin and edeine) do not affect the degradation and (b) dsRNA and ATP enhance RNA degradation also in the 200,000 x g supernatant fraction from extracts of interferon-treated cells and this fraction is essentially free of ribosomes. (The ribosome concentration in our 200,000 x g supernatant fraction is less than 1% of that in the 30,000 x g extract.) GTP or the ATP analogs adenosine 5'-(alpha,beta-methylene)triphosphate or adenosine 5'-(beta,gamma-methylene)triphosphate do not substitute for ATP, and dsDNA or DNA RNA hybrids do not substitute for dsRNA in activating endonuclease(int). The optimal concentration of ATP in activating endonuclease(int) is 1 mM or higher. The addition of dsRNA and ATP to extracts from interferon-treated cells affects the degradation of some RNAs much more than that of others. Thus it promotes the degradation of reovirus mRNA from the large size class strongly, the degradation of those from the medium size class to an intermediate extent and that of those from the small size class the least. Furthermore it enhances the degradation of mRNA from either control of interferon-treated Ehrlich ascites cells more than that of Ehrlich ascites cell ribosomal RNA or mouse globin mRNA. Reovirus dsRNA is not cleaved by endonuclease(int). The partially purified mouse interferon preparation (specific activity 8 x 10(8) NIH reference standard units/mg protein) used in several experiments was free of nuclease activity under our experimental conditions. Moreover the addition to extracts from control cells (or extracts from interferon-treated cells) of this interferon preparation together with dsRNA and ATP did not enhance nuclease activity. (Author abstract) (45 Refs)

61. INTERFERON TREATMENT OF EHRLICH ASCITES TUMOR CELLS: EFFECTS ON EXOGENOUS MRNA TRANSLATION AND TRNA INACTIVATION IN THE CELL EXTRACT.

Sen GC, Gupta SL, Brown GE, Lebleu B, Rebello MA, Lengyel P
Dept. Molecular Biophysics Biochemistry, Yale Univ., New Haven, CT 06520
J Virol; 17(1):191-203 1976

The effect of added crude tRNA on extracts of Ehrlich ascites tumor cells pretreated with partially purified mouse interferon preparations and passed through Sephadex G25 are described. The extracts from interferon-treated cells (S30int) compared to control extracts (S30c) have an impaired ability to translate exogenous mRNA (both host and encephalomyocarditis (EMC) viral), and this impairment can be overcome to a large extent by the addition of crude tRNA from Ehrlich ascites tumor cells but not that from Escherischia coli. The rate of inactivation of tRNAs specific for leucine, lysine, and serine was greater in S30int than in S30c; smaller effects were found with isoleucine, phenylalanine, and tyrosine. This increased rate of inactivation in S30int may explain the need for added RNA to partially overcome the impaired translation in these extracts. The amount of tRNA necessary to overcome the impaired translation of EMC viral RNA in S30int was essentially the same, whether the source of the tRNA was interferon-treated cells or normal cells. No difference in the rate of inactivation of leucine-specific tRNA in S30int was observed for tRNAs derived from interferon-treated and normal cells. Extracts of interferon-treated cells did not inactivate tRNAs specific for leucine and lysine unless the extracts had been passed through Sephadex G-25 or dialysed. However, the translation of exogenous mRNA was impaired in an extract of interferon-treated cells which had not been passed through Sephadex G-25, and this impairment was not overcome by added tRNA. (45 refs)

62. INCREASED ENDONUCLEASE ACTIVITY IN AN EXTRACT FROM MOUSE EHRLICH ASCITES TUMOR CELLS WHICH HAD BEEN TREATED WITH A PARTIALLY PURIFIED INTERFERON PREPARATION: DEPENDENCE ON DOUBLE-STRANDED RNA.

Brown GE, Lebleu B, Kawakita M, Shaila S, Sen GC, Lengyel P
Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, CT 06520
Biochem Biophys Res Commun; 69(1):114-122 1976

Reovirus messenger RNAs are degraded faster in crude extracts (S30) from mouse Ehrlich ascites tumor cells which have been treated with either a partially purified interferon preparation or the interferon inducer poly(I);poly(C) than in corresponding extracts from untreated cells. The faster degradation appears to be a consequence of endonuclease action. The endonuclease activity in vitro depends on the presence of double-stranded reovirus RNA in the reaction mixture. The results suggest a novel way in which double stranded RNA might be involved in mediating the function of an interferon system.

63. FORMATION AND CHARACTERISTICS OF REOVIRUS SUBVIRAL PARTICLES IN INTERFERON-TREATED MOUSE L CELLS.

Galster RL, Lengyel P
Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, CT 06520
Nucleic Acids Res; 3(3):581-598 1976

The early phase of reovirus replication in interferon-treated L cells (mouse L 929 fibroblasts) was examined. There was no difference in the adsorption of virus to cells, the rate and extent of conversion of parental virions to subviral particles (SVPs), and the protein and double-stranded RNA composition of the SVPs when reovirus infection of interferon-treated cells were compared to control cells. Furthermore, when tested in vitro, SVPs isolated from interferon-treated cells (SVPINT) synthesized and methylated reo mRNAs at the same rate as SVPs isolated from control cells (SVPCON). However, the accumulated products of RNA synthesis promoted by SVPCON consisted mainly of shorter products. These results indicate that premature termination of transcription and/or degradation of full size transcripts occurred in vitro with SVPINT.

64. REGULATION OF VESICULAR STOMATITIS VIRUS SPECIFIC PROTEIN SYNTHESIS IN INTERFERON TREATED MURINE CELLS (MEETING ABSTRACT).

Jungwirth C, Paraysz C, Billelo J, Koch G
Institut fur Virologie und Immunbiologie, Universitat Wurzburg, Wurzburg, W. Germany
J Clin Hematol Oncol; 9(4):281 1979

The effect of interferon was studied on the synthesis of vesicular stomatitis virus (VSV) specific proteins in Friend virus transformed mouse erythroleukemia cells and in mouse L-cells. In both cell lines VSV specific protein synthesis was inhibited reproducibly by pretreatment of the cells for 16 hr in concentrations of 1-20 units/ml. A similar concentration of chick interferon has been found to be inhibitory for VSV protein synthesis in chick embryo fibroblasts aged in culture. In contrast pretreatment of mouse erythroleukemia cells with interferon doses up to 1,000 units/ml did not inhibit synthesis of p 30 and gp 69 protein of the Friend virus. These results are compared to the interferon concentrations required to induce anticellular activities and the in vitro translation block in cell free extracts prepared from mouse L- and erythroleukemic cells. (no Refs)

65. METHYLATION OF VACCINIA VIRUS-SPECIFIC MRNA IN THE INTERFERON-TREATED CHICK CELL.

Kroath H, Janda HG, Hiller G, Kuhn E, Jungwirth C, Gross HJ, Bodo G
Institut fur Virologie und Immunbiologie, Universitat Wurzburg, Versbacher Strasse 7, 8700 Wurzburg, W. Germany
Virology; 92(2):572-577 1979

Results obtained with cell-free protein-synthesizing systems imply a mediating role of the methylated 5'-terminal 'cap' structure in the regulation of poxvirus-specific protein synthesis. In order to study a possible involvement of methylation in the interferon-induced inhibition of virus-specific protein synthesis in Vaccinia-infected cells, the extent of methylation of Vaccinia messenger (m)RNA synthesized in interferon and control chick embryo fibroblasts was compared. Induction of the antiviral state by pretreatment of chick cells with homologous interferon does not markedly reduce the degree of overall methylation of virus-specific mRNAs. Besides the two predominant 'cap I' structures m7 GpppAmpN and m7 GpppGmpN, 'incomplete' structures m7 GpppA and m7 GpppG can be detected in Vaccinia mRNA isolated from interferon-treated as well as from control cells. The ratio of complete to incomplete 'cap I' structures is decreased in the viral RNA from interferon-treated cells. This qualitative change in 'cap' methylation seems not to be limited to virus-specific mRNA. Possible implications of these findings on translational control in the interferon-treated cell are discussed. (Author abstract) (21 Refs)

66. RNA METHYLATION IN VACCINIA VIRUS-INFECTED CHICK EMBRYO FIBROBLASTS TREATED WITH HOMOLOGOUS INTERFERON.

Kroath H, Gross HJ, Jungwirth C, Bodo G
Institut fur Virologie, Immunbiologie der Universitat, Vienna, Austria
Nucleic Acids Res; 5(7):2441-2454 1978

Interferon-pretreatment of vaccinia-infected chick embryo fibroblasts resulted in a greater than 50% decrease in ribose methylation of penultimate 'cap' nucleotide in virus-specific messenger (m)RNA. However in contrast to results obtained with cell-free systems, in intact infected cells there was (a) no detectable reduction in methylation of the 5'-ultimate 7-methyl guanosine of viral mRNA; (b) a virus specificity of the interferon-induced change in mRNA 'cap'-methylation seems unlikely and (c) analysis of the ribosomal and transfer RNA fractions isolated from interferon-treated and control cells revealed identical patterns of methylated nucleotides. Thus, the interferon-induced change in methylation is specific for mRNA 'caps'. (Author abstract) (32 Refs)

67. EFFECT OF INTERFERON ON POXVIRUS REPLICATION.

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Institut fur Virologie und Immunbiologie, Universitat Wurzburg, D-8700 Wurzburg, W. Germany
Tex Rep Biol Med; 35:247-259 1978

Earlier observations on the effect of interferon on poxvirus replication are reviewed, and recent developments in this area of research are described. Pretreatment of animal cells with homologous interferon induces a more or less antiviral state against various strains of poxviruses. This results in an inhibition of virus replication and considerable protection of the host cell against virus-specific cytopathic effects. Treatment of chick embryo fibroblasts with interferon for several hours before viral infection resulted in a *concentration-dependent inhibition of virus-specific protein synthesis.* In general, the synthesis of many 'late' poxvirus-specific proteins appeared to be more sensitive to interferon than synthesis of 'early' virus-specific proteins. Poxvirus-specific DNA synthesis was relatively insensitive to interferon treatment. Observations made in other virus cell systems indicate that interferon acts intracellularly and inhibits poxvirus-specific gene expression. Studies in intact cells prove, with certain reservations, that virus-specific protein synthesis is specifically inhibited at the level of messenger RNA (mRNA) translation. Interferon produced no detectable structural alteration of poxvirus-specific mRNA. The molecular basis of the translation block and the discrimination between poxvirus-specific and cellular protein synthesis in interferon-treated cells remains unknown. (42 Refs)

68. INTERFERON-INDUCED TRANSLATION DEFECTS IN A CELL-FREE PROTEIN-SYNTHESIZING SYSTEM FROM MOUSE ERYTHROLEUKEMIA CELLS.

Mayr U, Parajsz C, Jungwirth C, Bodo G
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Virology; 88(1):54-61 1978

The mechanism of the interferon-induced translation inhibition was studied in vitro using a fractionated cell-free protein-synthesizing system prepared from Friend virus-transformed mouse erythroleukemia cells and L cells. The soluble fraction of the system was prepared from nonpreincubated 30,000 x gravity supernatants. To lower endogenous protein synthesis, the ribosomes were prepared from extracts treated with micrococcal nuclease at 20 C. If the components were prepared from interferon-treated cells, viral and cellular messenger (m)RNA translation was inhibited. In the cell-free system prepared from interferon-treated mouse erythroleukemia cells, the translation defect could be localized in the high-speed supernatant, while ribosomes from interferon-treated and control cells were of comparable activity. In contrast, ribosomes from interferon-treated L cells prepared by the same method were unable to support translation of exogenous mRNA. The interferon-induced translational defect in either cell-free system could not be overcome by adding transfer (t)RNA. Aminoacylation and stability of endogenous leucine-specific tRNA was not impaired in the high-speed supernatant of both of the

cell-free systems from interferon-treated cells. (Author abstract) (33 Refs)

69. RELEASE OF INTERFERON-INDUCED TRANSLATION INHIBITION BY TRNA IN CELL-FREE EXTRACTS FROM MOUSE ERYTHROLEUKEMIA CELLS.

Mayr U, Bernayer HP, Weidinger G, Jungwirth C, Gross HJ, Bodo G
Institut fur Virologie und Immunbiologie der Julius-Maximilians-Universitat Wurzburg, Versbacher Landstrasse 7, D-8700 Wurzburg, W. Germany
Eur J Biochem; 76(2):541-551 1977

A cell-free protein-synthesizing system prepared from Friend-virus-transformed mouse proerythroblasts was used to study the molecular mechanism of translation inhibition in cell-free extracts from interferon-treated murine cells and the antiviral effect of mouse interferon. In interferon-treated cell extracts, translation of globin and encephalomyocarditis virus (EMC) RNA was inhibited. The time point at which amino acid incorporation into peptides stopped depended on the strength of the interferon effect. The addition of tRNA from eukaryotic cells released the translation inhibition of EMC and globin RNA in extracts from interferon-treated cells. Various purified species of individual tRNAs were tested for activity to restore translation in these extracts. A mixture of isoaccepting leucine-specific tRNAs from rabbit liver was not able to compensate the translation inhibition; also inactive were tRNA1Val, tRNASer, and tRNA3Lys. Addition of tRNA2Lys, however, resulted in a translation of EMC RNA in extracts of interferon-treated cells. The compensating effect of this isoaccepting tRNALys was less than with unfractionated tRNA from eukaryotic cells indicating that other tRNAs must be present which can release the translation block. Data indicated that the amino acid acceptor function was not involved in the release of the translation inhibition, and that in an extract from interferon-treated cells in the presence of tRNA2Lys or tRNA treated with periodate, peptides synthesized had the same molecular wt as the smaller peptides in the reaction product synthesized with the extract from control cells. Run-off ribosomes from interferon-treated and control cells were of comparable activity in a fractionated cell-free system. When characteristics of the translation block in extracts from interferon-treated and vaccinia-infected mouse L-cells were compared, the block in interferon-treated and vaccinia-infected L-cells differed from that in uninfected extracts from interferon-treated murine cells. In the former cells, the translation inhibition cannot be released by addition of tRNA. The translation inhibition and release by tRNA in extracts from interferon-treated mouse proerythroblasts and uninfected mouse L-cells seem caused by the same molecular mechanism, but this phenomenon contrasts with inhibition of translation of exogenous mRNA seen in extracts from interferon-treated and vaccinia-infected L-cells. (45 Refs)

70. FAILURE OF GLOBIN MRNA TO STIMULATE GLOBIN SYNTHESIS IN CELL-FREE EXTRACTS OF INTERFERON-TREATED GLOBIN-SYNTHESIZING MOUSE ERYTHROLEUKEMIC CELLS.

Hiller G, Winkler I, Viehhauser G, Jungwirth C, Bodo G, Dube S, Ostertag W
Institut fur Virologie und Immunbiologie der Universita: Wurzburg, Wurzberg, W. Germany
Virology; 69(1):360-363 1976

Exogenous globin mRNA or encephalomyocarditis virus mRNA could be efficiently translated by S30 lysates of mouse erythroleukemic cells and by lysates of similar cells in which hemoglobin synthesis had been induced by dimethylsulfoxide. Cell-free extracts from interferon-treated cells had not only lost their translation capacity for viral but also for globin mRNA. The results suggest that the indiscriminate inhibition of the in vitro translation capacity of natural mRNA often seen in extracts from interferon-treated murine cells is caused by a defect of the cell-free systems. The defect in the S30 lysates of interferon-treated cells could be repaired by the addition of tRNA.

71. ALTERED OR INCREASED TRANSFER-RNA METHYLATION IN THE COURSE OF INTERFERON ACTION ON CELLS IN CULTURE?

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Experientia; 35(5):576-578 1979

The induction of the antiviral state by interferon might reflect the decrease of the rate of biosynthesis, the degradation or the alteration of one or several transfer (t)RNAs. This could result in rate-limiting concentrations for codons common in viral RNA but rare in host messenger RNA. Altered methylation of tRNA could be the basis of such a phenomenon. However, we could not find an altered extent of methylation of total tRNA or an altered pattern of methylation, if mixed tRNAs were chromatographed on methylated-albumin-Kieselgur- or BD-cellulose columns, despite a large range of conditions of pretreatment of chick embryo fibroblast cultures with interferon. (Author abstract) (25 Refs)

72. INHIBITION OF HERPES SIMPLEX VIRUS TYPE 1 SPECIFIC TRANSLATION BY POLY(I):POLY(C) INDUCED INTERFERENCE (MEETING ABSTRACT).

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Institut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, Postfach 820, D-7800 Freiburg, W. Germany
Abstracts of the 12th Meeting of the European Tumor Virus Group, held in Belgium, September 10-14, 1979, 1979.

Pretreatment with polyinosinic acid:polycytidylic acid in the presence of diethylaminoethanol-dextran induces in primary African green monkey kidney (pAGMK) cells antiviral resistance with concomitant release of interferon into the cell culture supernatant. Those pretreated and non-pretreated cells were infected with Herpes simplex virus type 1 (HSV1) in the presence of cytosine arabinoside (araC). The proteins were labeled with [35S]methionine from 6 to 10 hr post infection. The virus-specific proteins were immunoprecipitated with a pool of human sera exhibiting a titer against HSV1 early antigens and were analyzed in sodium dodecyl sulfate polyacrylamide gels. No virus-specific proteins could be detected under interference conditions, whereas more than 20 HSV1 proteins of the beta- and gamma-class could be demonstrated by immunoprecipitation from the extracts of the non-pretreated cells infected in the presence of araC. On the other hand, the intracellular concentration of HSV1-specific transcripts analyzed by liquid phase hybridization was not significantly altered under interference conditions. However, the transcription pattern of the HSV1-genome was restricted. A similar restriction could be affected, when protein synthesis was inhibited by cycloheximide. From these results we conclude that interferon regulates HSV1 replication mainly on the level of translation. (no Refs)

73. FIBROBLAST INTERFERON INDUCES SYNTHESIS OF FOUR PROTEINS IN HUMAN FIBROBLAST CELLS.

Knight E, Korant BD
Central Res. and Development Dept., Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, DE
Proc Natl Acad Sci USA; 76(4):1824-1827 1979

Treatment of human diploid fibroblasts with fibroblast interferon for 8 hr inhibited replication of vesicular stomatitis virus. When the total cell protein of cells treated with interferon for 8 hr was compared to the total cell protein of untreated cells by two-dimensional gel electrophoresis, the interferon-treated cells were found to contain four proteins not found in untreated cells. Addition of actinomycin D to the cells concurrently with interferon inhibited the synthesis of the four proteins. We conclude that these proteins are induced by interferon and that they may be involved in the inhibition of virus replication. (Author abstract) (14 Refs)

74. EFFECT OF INTERFERON ON SYNTHESIS OF VIRAL AND CELLULAR PROTEINS BY CHRONICALLY INFECTED MOUSE CELLS (MEETING ABSTRACT).

De Ley M, Billiau A, De Somer P
Rega Institute-K.U.Leuven, B-3000 Leuven, Belgium
J Clin Hematol Oncol; 9(4):286 1979

Interferon inhibits the production of C-type particles by chronically infected mouse cells. In order to investigate the modification brought about by the action of interferon in the released virus particles and in the cells rendered to the 'antiviral state', we have subjected radioactively labeled virus and cell lysates to sodium dodecyl sulfate-polyacrylamide gel electrophoresis and 2-dimensional electrophoresis. The virus particles isolated from the supernatant culture fluids, and purified by sucrose gradient ultracentrifugation, were enriched in a glycoprotein with a mol wt of 84,000 and an isoelectric point (pI) of 5.5, while their content of gp69/71 was decreased. The 84,000 dalton glycoprotein could not be immunoprecipitated with either anti-gp69/71 or with anti-p30. Interferon treatment also led to the induction in the cells of a 63,000 dalton protein with a pI of 6.3. The effect was already noticeable at 100 U/ml. The induction of the same protein in first passage mouse embryo fibroblasts argues for its cellular, rather than its viral origin. (no Refs)

75. COMPARATIVE ANALYSIS OF INTERFERON AND ANTIVIRAL PROTEIN MESSENGER RNAS.

Ershov FI, Sokolova TM, Tazulakhova EB, Kadyrova AA, Kisling U, Novokhatsky AS
D. I. Ivanovsky Inst. Virology, USSR Acad. Medical Sciences, 123098 Moscow, USSR
Acta Virol (Praha); 23(1):32-39 1979

A comparative analysis of interferon and antiviral protein messenger (m) RNAs was carried out. Differences in their biological activities and sedimentation coefficients were found. In RNA preparations from superinduced cells (cells treated with poly(I)-poly(C) and antimetabolites) and from cells treated with interferon, mRNAs possessing interferon and antiviral activities were detected. The results suggest the existence of two types of mRNA (for interferon and antiviral protein, respectively) and support the hypothetic model of interferon action via an antiviral protein. (Author abstract) (19 Refs)

76. STUDIES ON THE MECHANISM OF INTERFERON ACTION: CHARACTERIZATION OF POLYSOME-ASSOCIATED CELLULAR RNAS MODIFIED BY INTERFERON.

Riley FL, Levy HB
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014
Virology; 76(1):459-463 1977

Interferon-treated cells have the ability to translate normal cell messenger RNAs (mRNA) while being strongly restricted in their ability to translate viral mRNAs; the exact mechanism by which interferon-type ribosomes can distinguish between viral and cellular mRNAs is not understood. Recent reports show that interferon-induced alterations in RNA species are associated with polysomes in non-infected cells, and it was suggested that these modified RNAs are mRNAs and transfer RNAs (tRNA). The types of RNA that are altered and the nature of these alterations were studied using polyacrylamide gel electrophoresis in aqueous and nonaqueous medium of the CCL-1 strain of mouse L-cells to which interferon had been added. Highly reproducible differences in migration speeds between control and interferon-type RNAs were shown by the displacement of the curves. The tRNAs associated with interferon-type polysomes move more slowly than tRNAs from control cells. Transfer RNA species are much richer in methyl groups than other cellular RNA species. Areas of the gel in which mRNAs were found are much lower in methyl content, indicating that the fast-moving large peak is transfer RNA. These data agree with previous findings that interferon treatment of cells modifies certain restricted RNA fractions in cells, and support the conclusion that the polysome-associated RNAs that are altered are the mRNA and tRNA species. These data are consistent with the hypothesis that the interferon-treated cell has modified tRNAs and ribosomes that enable it to recognize and translate the modified mRNAs and reject the unmodified viral RNAs. (17 refs)

77. EFFECT OF INTERFERON ON CELLULAR RNA SYNTHESIS AND STRUCTURE.

Riley FL, Levy HB
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014
Tex Rep Biol Med; 35:239-246 1977

Recent reports dealing with the effect of interferon on cellular RNA synthesis and structure and other reports of cellular RNA modifications which may be related to the mechanism by which 'interferon-type' ribosomes are able to distinguish among different messenger RNAs (mRNA) are reviewed. Interferon inhibited multiplication of murine leukemia L1210 cells and significantly decreased the synthesis of total RNA and protein. In monolayers of mouse L cells, interferon treatment modified certain restricted RNA fractions in the cells. It was suggested that interferon treatment of cells leads to changes in cellular mRNAs such that the cells can distinguish them from the subsequently infecting viral RNA, and that transfer RNAs (tRNA) may also be involved. Characterization of the modified cellular RNAs showed that they are polyadenylic acid [poly(A)]-containing mRNAs, RNAs without a poly(A)-rich region and tRNAs. Data from electrophoresis on polyacrylamide gels were consistent with the hypothesis that interferon-treated cells develop modified mRNAs, which are different from both normal cellular mRNAs and viral mRNAs. In addition, modified tRNAs and ribosomes were observed in the interferon-treated cells. Recent findings indicate that tRNAs are involved in the interferon-induced antiviral state. Interferon-treated cells also show alterations in endonuclease activity,

phosphokinase activity, and nucleic acid methylation activity. Because of the lack of pure interferon, it does not seem possible to relate these different observations to a single general molecular mechanism. (24 Refs)

78. INTERFERON INHIBITION OF PROTEIN SYNTHESIS BY ISOLATED MITOCHONDRIA.

Kortsaris A, Taylor-Papadimitriou J, Georgatsos JG
Theagenion Cancer Inst., Serron 2, Thessaloniki, Greece
Biochem Biophys Res Commun; 68(4):1317-1322 1976

The effect of interferon on EMC virus RNA stimulated protein synthesis in mitochondria from L cells was investigated. The incorporation of H3-leucine into acid precipitable material was stimulated more than two-fold by 3 micrograms of EMC virus RNA. Cycloheximide had little or no effect on protein synthesis, while chloramphenicol, at 25 micrograms/ml, reduced the incorporation of label in the presence of EMC virus RNA by 80%. Pretreatment of L cells with mouse interferon (1600 units/ml) inhibited by 85% EMC-RNA stimulated protein synthesis. There was no difference in the uptake of radioactivity in labelled EMC mitochondria isolated from interferon treated or untreated L cells. In both cases, the fraction of TCA precipitable radioactivity associated with mitochondria after incubation was approx 1.5% of the total amount added. It is concluded that EMC-RNA can stimulate the incorporation of H3-leucine into protein in isolated mitochondria from L cells and that this stimulation of protein synthesis is reduced very significantly and reproducibly if the mitochondria are isolated from cells which have been treated with interferon. (10 refs)

79. EVIDENCE FOR A TRANSLATION-INHIBITORY RIBOSOME-ASSOCIATED PROTEIN.

Joklik WK
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
Tex Rep Biol Med; 35:264-269 1977

The mechanism by which interferon inhibits translation of viral messenger (m)RNAs is discussed. Interferon inhibition of translation of early viral mRNAs has been demonstrated in double-stranded-containing DNA and RNA viruses. In cell-free systems, this lack of translation of mRNAs has been shown to be due to an inhibitory factor that was associated with ribosomes and could be removed by washing with 0.5 M KCl. One of these cell-free protein-synthesizing systems has displayed the same ability to discriminate between host- and virus-specified mRNAs as interferon-treated cells. A cell-free protein-synthesizing system derived from Krebs ascites tumor cells was unable to translate viral (double-stranded DNA or RNA) mRNA after interferon treatment but did translate L cell of Krebs ascites mRNAs at the same rate as extracts of untreated cells. A 48,000 dalton polypeptide was present in 0.3-0.6 M and 0.6-1.0 M KCl washes of ribosomes from interferon-treated cells, but was absent or present in far lower amounts in washes from ribosomes from normal cells. Addition of the washes containing the 48,000 dalton polypeptide to protein-synthesizing extracts of normal cells inhibited the translation of viral mRNAs from double-stranded DNA and RNA viruses. It is not known whether this polypeptide is responsible for the inability of ribosomes from interferon-treated cells to translate viral mRNAs. (23 Refs)

80. SYNTHESIS OF TYPE-C VIRUS PARTICLES FROM MURINE CULTURED CELLS INDUCED BY IODODEOXYURIDINE. VI. BIOSYNTHESIS OF REVERSE TRANSCRIPTASE.

Reitz MS, Wu AM, Gallo RC
Litton Bionetics, Inc., 7300 Pearl St., Bethesda, MD 20014
Int J Cancer; 20(1):67-74 1977

The effects of dexamethasone (dex) and/or interferon (IF) on the biosynthesis of reverse transcriptase (RT) in 5-iodo-2'-deoxyuridine (IUdR)-induced BALB/3T3 cells nonproductively transformed with Kirsten murine sarcoma virus were studied. Dex stimulated the production of BALB virus-2 (v-2) and its Kirsten sarcoma virus pseudotype, but it did not increase the intracellular specific activity of RT. IF reduced v-2 production and decreased intracellular RT to barely detectable levels. Simultaneous treatment of induced cells with both dex and IF resulted in a level of intracellular RT equal to that of cells treated with IUdR alone, even though extracellular v-2 production was approx five-fold lower. In contrast, neither compound affected the synthesis of N-tropic BALB virus-1, which is produced later (5-7 days) after IUdR treatment, nor was there any decrease in intracellular RT at this time. These results indicate that dex and IF have both translational (or pretranslational) and posttranslational effects on the production of xenotropic (v-2) murine C-type virus. (30 Refs)

81. THE ANTIVIRAL ACTIVITY OF RNA PREPARATIONS ISOLATED FROM INTERFERON-TREATED CELLS (MESSENGER RNA FOR ANTIVIRAL PROTEIN?).

Orlova TG, Mamontova TV, Zhdanova LV, Soloviev VD
N. F. Gamaleya Inst. Epidemiology and Microbiology, Moscow, USSR
Biull Eksp Biol Med; 83(4):436-437 1977

The nature of newly synthesized RNA in chick embryo cells treated with interferon was examined. It was found that, after interferon treatment, these cells yielded a biologically active RNA. When this RNA was inoculated into chick embryo cells, and the levels of vesicular stomatitis virus reproduction assayed, it was found that the cells treated with this RNA exhibited virus levels 2 to 30% of the levels in cells treated with control RNA. Max antiviral activity of the experimental RNA was found at 3 hr after interferon treatment. (5 Refs)

82. INHIBITION BY INTERFERON OF SV40 TUMOR ANTIGEN FORMATION IN CELLS INJECTED WITH SV40 CRNA TRANSCRIBED IN VITRO.

Graessmann A, Graessmann M, Hoffmann H, Niebel J, Brandner G, Mueller N
Inst. Molecularbiol. Biochem., Freien U. Berlin, Germany
FEBS Lett; 39(3):249-251 1974

Simian virus 40 (SV40) cRNA was synthesized in vitro with E coli RNA polymerase and injected into monkey kidney cells (TC7) by means of a microinjection technique. The SV40 cRNA-injected cells showed SV40 T-antigen within 24 hours. This SV40 cRNA-induced T-antigen formation was not inhibited by actinomycin D (1 microg/ml), or by treatment of the cRNA with pancreatic DNase. RNase and alkaline treatment destroyed the biological activity of the cRNA. The arrangement of T-antigen in the nuclei induced by in vitro cRNA was the same as in the SV40 virus infected cells. When TC7 cells were treated with human interferon (2000 units/ml) 18 hours prior to cRNA injection, only 0.1% of the cells were positive for SV40 T-antigen 24 hours after RNA injection compared to 40% of the control (non-interferon-treated) cells. The rate of reduction of T-

antigen positive cells by interferon was in the same range when SV40 DNA was injected into the TC7 cells instead of virus cRNA. The data support the hypothesis that interferon inhibits primarily the translation of the SV40 genome.

83. INTERFERON AND CELL DIVISION. VIII. EFFECT OF INTERFERON ON MACROMOLECULAR SYNTHESIS IN L1210 CELLS IN VITRO.
Brouty-Boye D, Macieira-Coelho A, Fiszman M, Gresser I
Inst. Sci. Res. Cancer, Villejuif, France
Int J Cancer; 12(1):250-258 1973

L1210 cells of the interferon-sensitive (L1210 S; 2 x 10(5) cells/ml) and interferon-resistant (L1210 R; 2 x 10(5) cells/ml) cell lines were cultivated in the presence of purified interferon (320 U/0.2 ml) or purified control preparation. Interferon inhibited the multiplication of the L1210 S cells but did not affect L1210 R cells in this manner. Pulse labeling with 3H-uridine revealed max. RNA synthesis in L1210 S cells at 48 hr, as compared to 24 hr in controls; incubation in highly purified interferon further delayed peak RNA and protein synthesis. L1210 R cells remained unaffected by purified or highly purified interferon. Cultivation of labeled (3H-uridine for 3 hr) L1210 S cells in the presence of interferon for 12 hr did not affect polyribosome or ribosome formation; however, after 22 hr inhibition of polyribosome formation was detected but ribosomal units remained unaffected. As cells approached plateau growth, controls formed fewer polyribosomes while polyribosome formation persisted in L1210 S cells. Interferon did not inhibit the formation of polyribosomes in L1210 R cells. No effect was observed on the synthesis of ribosomal subunits in interferon-treated cells at a time when polyribosome formation was inhibited. This suggests that a decreased polyribosome formation may have been due either to a decreased synthesis of mRNA in interferon-treated cells or a decreased attachment of mRNA to polyribosomes, or both. It is postulated that a common mechanism may underlie both the antiviral effect of interferon and its effect on cell division and macromolecular synthesis. (32 refs)

84. INHIBITORY EFFECT OF CHICK INTERFERON AND INTERFERON INDUCER (RL:RC) ON THE INDUCTION OF CELLULAR DNA SYNTHESIS AND TRANSFORMATION OF CHICK EMBRYO FIBROBLASTS INFECTED IN CULTURE WITH ROUS SARCOMA VIRUS.
Kara J
Inst., Exp. Biol. Genetics, Czechoslovak Acad. Sci, Prague
Folia Biol (Praha); 19(3):194-202 1973

Chick embryo fibroblasts (CEF) preincubated for 24 hr in tissue culture with chick interferon and subsequently infected with Rous sarcoma virus (RSV), strain Schmidt-Ruppin, exhibit a significant resistance to the induction of cellular DNA synthesis after infection and a concomitant resistance to the transformation by RSV. The induction of uridine kinase activity and cellular DNA polymerase activity after RSV-infection is inhibited in CEF cultures pretreated with chick interferon. When RSV preparation purified by zonal centrifugation in sucrose density gradient was used for infection of CEF cultures, cellular DNA synthesis was activated and the inhibitory effect of interferon on the induction of cellular DNA synthesis and cell transformation was observed. Preincubation of CEF cultures for 4 hr in the presence of polyriboinosinic:polyribocytidylic acid (rI:rC, 20 microg/ml) resulted in complete inhibition of the induction of cellular DNA synthesis and 95% inhibition of cell transformation after infection of rI:rC pretreated cultures with RSV. The purified RSV, heat-inactivated for 5 min at 100 C, does not induce DNA synthesis in CEF cultures. These results suggest that induction of cellular DNA synthesis and cell transformation are virus-specific functions, very probably mediated by virus-specific proteins. The biosynthesis of the viral proteins seems to be inhibited in cells pretreated with interferon and/or with rI:rC.

D.
Effects of Interferons on Virus Maturation and Release

85. EFFECT OF INTERFERON ON MOUSE LEUKAEMIA VIRUS (MULV). V. ABNORMAL PROTEINS IN VIRIONS OF RAUSCHER MULV PRODUCED IN THE PRESENCE OF INTERFERON.
Pitha PM, Fernie B, Maldarelli F, Hattman T, Wivel NA
Lab. Biochemical Virology, Johns Hopkins Univ. Cancer Center, Baltimore, MD
J Gen Virol; 46(1):97-110 1980

Interferon treatment of JLSV-6 cells chronically infected with Rauscher MuLV leads to the formation of noninfectious particles ('interferon' virions) containing the structural proteins coded by the envelope (env) and gag genes as well as additional virus polypeptides. The major glycoprotein detected in the control virions is gp71, but 'interferon' virions contain, in addition, an 85,000 mol wt (gp85) glucosamine-containing, fucose-deficient glycoprotein. This is recognized by antiserum to MuLV and may be related to env pr85. Surface iodination of intact virions indicates that gp71 and gp85 are the two major components of the external envelope. However, whereas in control virions gp71 associates with pi5E (gy90), this complex was not detected in 'interferon' virions. Analysis of radio-labeled (3H-amino acids or iodinated) proteins from disrupted 'interferon' virions revealed the presence of 65,000, 55,000, 40,000, 20,000 and 12,000 mol wt polypeptides which could be precipitated with antiserum against MuLV. There was a distinct difference in the patterns of incorporation of pulse-labeled 3H-amino acid polypeptides into virions in the presence and absence of interferon. Those polypeptides labeled in the presence of interferon and recovered in the extracellular virions in a chase with interferon appeared to have substantially fewer copies of p30 and more of gag pr55 polypeptide than in controls. These results indicate that in the presence of interferon there are changes in the proteolytic cleavage associated with virion assembly. (Author abstract) (43 Refs)

86. THE ERRORS IN ASSEMBLY OF MULV IN INTERFERON TREATED CELLS.
Pitha PM, Fernie B, Maldarelli F, Wivel NA
Lab. Biochemical Virology, Johns Hopkins Univ. Oncology Center, Baltimore, MD
J Supramol Struct; 12(1):35-46 1979

The viral polypeptides of murine leukemia virus (MuLV) virions produced in JLSV-6 cells in the presence and absence of interferon (IF) were studied using high-resolution sodium dodecyl sulfate polyacrylamide gel electrophoresis and immunoprecipitation with antisera against viral proteins of the gag and env genes. Virions assembled in the presence of IF contained greater amounts of peptides corresponding in mobility to p15E and gag pr65, and had additional bands present in the 72-90,000, 40-50,000, and 30-35,000 regions. The amount of p30 in the virions assembled in the presence and absence of IF was similar. Precipitation with antisera of MuLV p30 and gp71 indicated that the virions produced in the presence of IF contained at least two high-mol-wt proteins (83,000 and 65,000) which were not present in the con-

trol virions. Surface iodination of the control virions revealed gp71 as the major band with minor bands in the gp45 and gp32 regions, whereas only gp71 was present on the virions assembled in the presence of IF. The rates of synthesis and processing of viral proteins in IF-treated and control cells were comparable. The data indicate that erroneous virus assembly occurs in the presence of IF and that this leads to inhibition of virus release and decreased viral infectivity. (28 Refs)

87. EFFECT OF INTERFERON ON MURINE LEUKAEMIA VIRUS INFECTION. IV. FORMATION OF NONINFECTIOUS VIRUS IN CHRONICALLY INFECTED CELLS.

Pitha PM, Wivel NA, Fernie BF, Harper HP
Oncology Center, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
J Gen Virol; 42(3):467-480 1979

SC-1 and AKR-2B mouse cells that were chronically infected with murine leukemia virus (MuLV) were treated with interferon (IF: 150 units/ml), and the number of cell-associated virions and released virions produced before and after treatment was compared, along with their infectivity, content of virus genome RNA, and morphology. IF treatment led to a 100-fold decrease in the amount of infectious virus released into the medium and a 10-fold decrease in the number of virus particles measured by the virion-associated reverse transcriptase assay. However, there was little change in the amount of cell-associated infectious virus, although nearly twice as many cell-associated virions were counted in electron micrographs. With both types of cells, IF blocked MuLV replication at the postbudding stage, but it did not change the morphology of the particles produced or their content of virion 70S RNA. Infectious virus assembled on the cell membranes of IF-treated cells was less stable at 37 C than that grown in the absence of IF. Release of infectious virus from IF-treated cells was not inhibited by actinomycin D or cycloheximide, although both agents inhibited virus production in controls. These results show that IF inhibits MuLV replication through effects on virion assembly; these effects lead to the formation of noninfectious particles and of fewer virions. Kinetics analysis further shows that IF affects MuLV assembly rapidly, and the induction of an antiviral protein may not be required. (34 Refs)

88. INTERFERON EFFECT ON MULV INFECTION: FORMATION OF UNINFECTIOUS VIRUS IN CHRONICALLY INFECTED CELLS (MEETING ABSTRACT).

Pitha PM, Wivel NA, Fernie BF
Johns Hopkins Oncology Center, Baltimore, MD, 21205
J Supramol Struct; (Suppl 2):252 1978

Treatment of SC-1 cells chronically infected with murine leukemia virus (MuLV) with interferon (150 units/ml) leads to a 100-fold decrease in the amount of infectious virus in the medium, but only to a 10-fold decrease in the number of released virus particles. In the cells the amount of infectious virus was not greatly affected, while the number of cell-associated virions quantitated by electron microscopy was 2-5 fold higher in interferon-treated cells than in the controls. The interferon block of MuLV replication occurred at the *post-budding stage*, and the virus particles produced in the presence and absence of interferon were morphologically indistinguishable. Interferon had no effect on the transcription of viral RNA, and interferon-treated particles contained 70 Svedberg (S) RNA and all the major structural proteins. The particles synthesized in the presence of interferon contained 3 novel polypeptides. Two of these are glycosylated (mol wt 85,000 and 68,000), and one (mol wt 70,000) is glucosamine deficient. The ratio of the relative amounts of protein (p)30/glycoprotein (gp)71 in the virions made in the presence of interferon is 3 fold higher than in the control virus. The pulse-chase experiments demonstrated that the precursor synthesized in the presence of interferon could be cleaved and assembled into the virions after interferon removal. These results show that the interferon-induced inhibition of MuLV replication is due to a deficiency in the virion assembly which leads both to the formation of uninfectious particles and to the decrease in virion production.

89. EFFECT OF INTERFERON ON MURINE LEUKEMIA VIRUS INFECTION. II. SYNTHESIS OF VIRAL COMPONENTS IN EXOGENOUS INFECTION.

Pitha PM, Staal SP, Bolognesi DP, Denny TP, Rowe WP
Oncology Center, Johns Hopkins Univ., Sch. Medicine, Baltimore, MD 21224
Virology; 79(1):1-13 1977

The effect of interferon on acute exogenous infection with AKR mouse leukemia virus (MuLV) was investigated by examining parameters of the virus replication. Included were studies of the effect of interferon on synthesis of viral RNA, gp71, and precursor protein, and on the ability of the cells to induce XC cell syncytium formation. The effect of interferon on individual steps of MuLV replication was studied during a single cycle of infection; none of these was inhibited to such an extent as to cause the observed 200-fold inhibition of infectious virus production. In the single step AKR-L1 virus replicative cycle, the whole provirus genome was transcribed in interferon-treated cells as measured by hybridization with a [H]DNA probe made from AKR virus. Interferon-treated cells synthesized somewhat less viral RNA (36%) than controls, which may represent a slight quantitative difference between these cells or the absence of a special subclass of viral RNA. Translation of viral mRNA was also relatively unaffected by interferon; synthesis and processing of the major viral core protein (p30) was not visibly affected by interferon treatment. Synthesis of proteins p15 and p12 was also probably not affected. Synthesis of the major viral glycoprotein gp71 was inhibited 2-5 x by interferon, but this degree of inhibition probably could not have caused the decrease in production of infectious virus. The ability of interferon-treated cells to induce XC cell fusion provides additional evidence that most of the MuLV synthetic events are normal after interferon treatment. Results suggest that interferon-induced inhibition of MuLV replication occurs in two steps: a relatively inefficient first block affecting an early step in replication and the major effect which affects late events in virus development. The latter effect is seen in both acute and chronic MuLV infection, and it occurs after synthesis of viral mRNA, p30, and gp71 but before virus assembly or maturation. (40 Refs)

90. EFFECT OF INTERFERON ON EXOGENOUS, ENDOGENOUS, AND CHRONIC MURINE LEUKEMIA VIRUS INFECTION.

Pitha PM, Rowe WP
Oncology Center, John Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Prog Cancer Res Ther; 2:361-367 1977

The effect of purified mouse interferon on the replication of AKR murine leukemia virus (MLV) in a clonal line of AKR cells was studied, with emphasis on comparing the effect of interferon on the replication of exogenous virus, the induction of endogenous virus, and the production of virus by chronically infected cells. Interferon was found to

inhibit virus replication in all three systems. Interferon did not abort exogenous infection or virus induction; rather, it only delayed the appearance of infectious virus. Virus production by chronically infected cells was also suppressed in the presence of interferon; however, after removal of interferon, rapid recovery of virus production occurred. Under conditions where interferon treatment inhibited virus yield, as measured both by infectious virus and virion-associated reverse transcriptase activity, no significant inhibition of the synthesis of virus-specific (gs) antigen was observed. These results indicate that, unlike its effect on the majority of lytic viruses, interferon does not inhibit MLV by a general inhibition of viral protein synthesis. Rather, it appears to inhibit one or more of the later steps in MLV replication which occur after the expression of viral gs antigen. (27 Refs)

91. EFFECT OF INTERFERON TREATMENT ON CELL MEMBRANES.

Friedman RM, Maheshwari RK, Jay FT, Czarniecki C
Lab. Experimental Pathology, NIH, Bethesda, MD
Fed Proc; 40(2):208-209 1981

Two effects of interferon treatment on virus growth are discussed: an adherence of virus particles to the plasma membrane of cells; and the production of virus particles of extremely low infectivity. It was concluded that the deficiency of glycoprotein in interferon-treated cells may be related to the inhibition of its glycosylation. (3 Refs)

92. INTERFERON TREATMENT INHIBITS GLYCOSYLATION OF A VIRAL PROTEIN.

Maheshwari RK, Banerjee DK, Waechter CJ, Olden K, Friedman RM
Lab. Experimental Pathology, NIAMDD, NIH, Bethesda, MD, 20205
Nature (Lond); 287(5781):454-456 1980

In mouse L cells infected with vesicular stomatitis virus (VSV), exposure to purified mouse interferon (IF: 30 reference units/ml) reduced the production of infectious VSV by 200-fold. Exposure to tunicamycin (TM: 0.5 or 1.0 ug/ml) caused a concentration-dependent reduction in VSV production (10-80-fold). The IF-exposed cells showed biochemical and morphologic evidence of a significant reduction in glycoprotein (GP) and membrane protein (MP) of the released VSV particles. The TM-exposed VSV also showed reduced GP and MP concentrations, as well as a protein resembling an unglycosylated GP. Both IF and TM inhibited an early step in the formation of the asparagine-linked oligosaccharide chains: the incorporation by the membranes of treated cells of N-acetylglucosamine into glycolipids with the properties of dolichol derivatives. (29 Refs)

93. STRUCTURAL ABNORMALITIES IN MURINE LEUKEMIA VIRUSES PRODUCED BY INTERFERON-TREATED CELLS.

Bandyopadhyay AK, Chang EH, Levy CC, Friedman RM
NCI, Baltimore Cancer Res. Center, Baltimore, MD, 21201
Biochem Biophys Res Commun; 87(4):983-988 1979

The structure of the virus protein-protein complex between viral p30 antigen and reverse transcriptase in Moloney murine leukemia virus (MMLV) particles produced in interferon-treated mouse TB cells was investigated as part of a study to explain the decreased infectivity of virus particles isolated from these cells. In virus pools containing approx the same concentration of virus (as evidenced by the concentration of group specific or p30 viral antigen) there was, in MMLV from interferon-treated cells, a decrease in reverse-transcriptase activity with 70 Svedberg unit (S) viral RNA as a template; however, no significant decrease was observed with deoxythymidine (dT)12-ribosyladenine (rA)n as a template. An analysis of Triton X-100 treated MMLV on glycerol gradients revealed that on gradients containing MMLV from interferon-treated cells, the amount of the approx 18 S complex containing reverse-transcriptase and p30 antigen was greatly reduced. Furthermore, most of the p30 activity was found at the top of the gradient while peaks of reverse transcriptase activity were located in several regions of the gradient, only in one (at approx 18 S) of which it co-sedimented with p30. The results point to a defective complex between p30 antigen and reverse-transcriptase in these interferon-treated cells which possibly accounts for part of the decreased infectivity of these virus particles. (15 Refs)

94. INTERFERON INHIBITS MOUSE LEUKAEMIA VIRUS RELEASE: AN ELECTRON MICROSCOPE STUDY.

Chang EH, Mims SJ, Triche TJ, Friedman RM
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD 20014
J Gen Virol; 34(2):363-367 1977

The effect of interferon on AKR cells chronically infected with AKR mouse leukemia virus is described. Transmission electron microscopy of AKR, C+ and C- cells found intra- and extracellular C-type virus, with or without interferon (IF) treatment, although the number of extracellular particles was reduced after IF. About 80% of the particles in IF-cells were budding virions, compared with 30% for untreated cells. Because of the low extracellular virus production of IF cells, the large number of associated budding virions is puzzling. In scanning electron microscope studies, the C+ cells had fewer microvilli than the C- cells, except in mitosis. Virus particles were more numerous on the surface of IF than on untreated cells. Although reverse transcriptase assay found extracellular virus decreased, intracellular virus and virus group-specific (p 30) antigen were equal to or higher in IF-C+ cells than untreated cells, suggesting that the virus genome is partially expressed in IF cells. The data indicate that IF activity is restricted to a late stage in virus assembly or virus release. (18 refs)

95. THE EFFECT OF INTERFERON ON DE NOVO INFECTION OF MOLONEY MURINE LEUKEMIA VIRUS.

Wong PK, Yuen PH, MacLeod R, Chang EH, Myers MW, Friedman RM
Dept. Microbiology, Univ. Illinois, 131 Burrill Hall, Urbana, IL 61801
Cell (Camb); 10(2):245-252 1977

Cultured thymus and bone marrow (TB) cells from CFW/D mice were infected in suspension with either wild-type Moloney murine leukemia virus (MLV) or a temperature-sensitive mutant (ts 3) of MLV. Cultures were treated with 100 units/ml mouse interferon at time of infection. After incubation at 39 C for 24 hr, cultures were assayed for reverse transcriptase activity and infectious virus. Interferon treatment of MLV-infected cultures resulted in a 2,000-fold decrease in the production of infectious MLV, but only a 10 to 20-fold decrease in reverse transcriptase activity. Scanning electron microscopic examination of interferon-treated cells indicated a 2-fold decrease in the number of virus particles associated with the cell membrane. Transmission electron microscopic observations indicated a higher proportion of early budding virions to later stages of assembly in interferon-treated cells. Release of ts 3 virions, which fail to dissociate from the cell surface at the non-permissive temperature, was not inhibited by interferon treatment (100 units/

ml, 48 hr after infection by ts-3) when cultures were shifted to the permissive temperature 26 hr after interferon treatment. Results suggest that interferon does not inhibit late stages of virion assembly or virion release. In interferon-treated cells, the majority of virions produced are non-infectious. Inhibitory effects of interferon on de novo MLV infection of TB cells appeared to be more pronounced than effects on chronic infection of MLV in the same system. (27 refs)

96. INHIBITORY EFFECT OF INTERFERON ON A TEMPERATURE-SENSITIVE MUTANT OF MOLONEY MURINE LEUKEMIA VIRUS.

Chang EH, Myers MW, Wong PK, Friedman RM
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, and Digestive Disease, NIH, Bethesda, MD 20014
Virology; 77(2):625-636 1977

The effects of interferon (IF) treatment on mouse thymus and bone marrow (TB) cells chronically infected with ts3, a temperature-sensitive mutant of Moloney murine leukemia virus (MuLV), are reported. A minimum of 20 hr of exposure to IF was necessary to inhibit cell growth markedly. No significant difference in cell number was observed among cultures treated with various concentrations of IF for 26 hr. Cultures exposed to IF showed an altered pattern of virus release. Using a reverse transcriptase assay, it was discovered that there was a > 70% inhibition of virus release during the first 10 min following a drop in temperature from 39 to 34 C. The amount of extracellular virus increased tenfold between 10 and 20 min. There was a significant lag in virus release in the 20- to 30-min time period. Virus release resumed after 30 min, but it was inhibited 50%-75% compared to controls. The results of varying the duration of IF suggest that IF inhibits some late stage of virus assembly. The temperature-sensitive step of virus assembly follows the IF step. The effect of IF on intracellular group-specific antigen (p30) was also studied. The level of p30 was consistently higher in cells grown at the nonpermissive temperature (39 C) than in cells grown at the permissive temperature (34 C). IF lowered the concentration of p30 in cells grown at 39 C, but it had no effect on p30 concentration in cells grown at 34 C. Analysis of virus yields by several parameters indicated that IF treatment at 39 C resulted in the release of noninfectious viral particles. (16 Refs)

97. INTERFERON-DIRECTED INHIBITION OF CHRONIC MURINE LEUKEMIA VIRUS PRODUCTION IN CELL CULTURES.

Friedman RM, Jay FT, Chang EH, Myers MW, Ramseur JM, Mims SJ, Triche TJ, Wong PK
Lab. Experimental Pathology, Natl. Inst. for Arthritis, Metabolism and Digestive Diseases, Bethesda, MD, 20014
Prog Cancer Res Ther; 2:347-359 1977

Recent studies on the inhibition of murine leukemia virus (MLV) by interferon are reviewed. Interferon at concentrations of 10 and 30 international mouse reference units/ml inhibited MLV production in cultures of AKR mouse fibroblasts. However, intracellular concentrations of viral p30 (gs) antigen and viral reverse transcriptase were not decreased, and in the case of the p30 antigen were actually increased. These findings are due to an inhibition of virus release from the cell surface into the extracellular fluid, a phenomenon that was assayed by scanning electron microscopy. Studies with the late temperature-sensitive ts-3 mutant of MLV suggested that the interferon-sensitive locus is before or, possibly, is the same as the ts-3 site. (11 Refs)

98. INHIBITION OF MURINE LEUKEMIA VIRUS PRODUCTION IN CHRONICALLY INFECTED AKR CELLS: A NOVEL EFFECT OF INTERFERON (MEETING ABSTRACT).

Friedman RM, Ramseur JM
Lab. Exp. Pathol., Natl. Inst. Arthritis, Metab., Digest. Dis., N.I.H., Bethesda, Md.
Proc Natl Acad Sci USA; 71(9):3542-3544 1974

The effect of interferon on AKR mouse cells which have spontaneously become producers of murine leukemia virus was determined. The mouse cells (AKR, C1) contained the viral genome, produced virus, viral reverse transcriptase, and viral p30(gs) antigen, whereas previously they were negative for virus production and the presence of viral p30 antigen and reverse transcriptase activity. Purified mouse interferon produced in rabbits (> X 10 IU/mg protein)(1-80 IU/ml) had a specific antiviral effect against these AKR, C1 mouse cells, was stable to pH 2, was destroyed by heating to 65– or treatment with trypsin, and was not removed by washing. At the conc used, the viral reverse transcriptase was inhibited, and at the highest conc viral infectivity was reduced from 5.8 to 3.8 log10/ml. The effect of interferon decreased over 72 hr, and an increase in cellular viral (gs) antigen from 0.96 to 5.9 ug/mg protein occurred at an interferon conc of 30 IU/ml. This suggests that inhibition of viral assembly or release in AKR mouse cells was mediated by interferon treatment of the host cell system. (11 refs)

99. INTERFERON-INDUCED CHANGES IN RAUSCHER LEUKEMIA VIRUS PRODUCED BY CHRONICALLY INFECTED MOUSE CELLS (MEETING ABSTRACT).

De Ley M, Billiau A, De Somer P
Rega Inst., Katholieke Universiteit Leuven, B-3000 Leuven, Belgium
Abstracts of the 12th Meeting of the European Tumor Virus Group, held in Belgium, September 10-14, 1979, 1979.

Interferons are antiviral glycoproteins produced by cells after contact with a virus. They inhibit virus production both in exogenous and endogenous infections. The antiviral mechanism was studied by investigating the influence of mouse interferon on the production of C-type particles by chronically infected mouse cells (JLSV5 and L-1210). Treatment of JLSV5-cells with mouse interferon results in a reversible inhibition of the virus production (to less than 10%). This inhibition is situated at a late stage in the virus assembly and/or release. In addition, the virus particles produced in the presence of interferon are non-infectious. In order to investigate the molecular modifications brought about by the action of interferon, we have subjected radioactively labeled virus to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and 2-D-electrophoresis. SDS-PAGE showed that the treatment with 10(3) units/ml mouse interferon resulted in the selective decrease of a 72,000 dalton protein in 35S-L-methionine or 3H-amino acid-labeled virus particles. Simultaneously, an 84,000 dalton protein (only present to a very low extent in particles from control cells) was markedly increased. Labeling with 14C-glucosamine showed both to be glycoproteins. The purified virus particles were also subjected to 2-D-electrophoresis (isoelectric focusing followed by SDS-PAGE). While the 72,000 dalton protein (gp69/71) consisted of a heterogeneous population (isoelectric point (pI) from 6.8 to 7.5), the gp84 was composed of only one protein species with a pI of 5.5. (no Refs)

100. INTERFERON INHIBITS C-TYPE VIRUS AT A POSTTRANSCRIPTIONAL, PRERELEASE STEP.
Billiau A, Heremans H, Allen PT, Baron S, De Somer P
Dept. Human Biology, Div. Microbiology, Rega Inst., Univ. Leuven, Leuven, Belgium
Arch Virol; 57(3):205-220 1978

The mode of action of interferon in JLSV 5-cells, chronically infected with Rauscher murine leukemia virus (MLV), was studied by examining the fate of preexisting labeled viral RNA in interferon-treated cells and by determining the infectivity/physical particle ratio of cell-associated and extracellular virus. Interferon added together with 3H-uridine inhibited the production of labeled virus particles even when it was only allowed to act after all viral RNA synthesis had been stopped by actinomycin D. This indicated that the interferon-induced antiviral state primarily functions at a posttranscriptional step. When interferon was given after a 3H-uridine pulse label and arrest of label incorporation by glucosamine and unlabeled uridine, it prevented a portion of the preexisting radioactive RNA from occurring in extracellular particles. However, part of the labeled viral RNA had reached a stage beyond which interferon could not prevent it from occurring in extracellular virus particles. The notion that interferon primarily affects release of fully assembled and enveloped MLV particles may be eliminated: interferon-treatment did not affect the release of particle-bound reverse transcriptase in cells treated with cycloheximide after the antiviral state had been established. It was confirmed that interferon-treated JLSV 5-cells contained an increased number of virus particles associated with the cell membrane. However, these particles were found to have a reduced infectivity compared to those associated with control cells, thus confirming the view that virions produced by interferon-treated cells are defective; perhaps lacking in certain components. (Author abstract) (29 Refs)

101. EFFECT OF INTERFERON ON RNA TUMOR VIRUSES.
Billiau A
Dept. Human Biology, Div. Microbiology, Rega Inst., Univ. Leuven, B-3000 Leuven, Belgium
Tex Rep Biol Med; 35:406-419 1977

Studies investigating the effect of interferon on RNA tumor viruses are reviewed. Topics discussed include the following: the effect of interferon on primary infection, on drug-induced activation of C-type oncornaviruses, and on established steady state infection; the site of action of interferon in C-type virus infected cells; the defectiveness of C-type virus particles produced by interferon-treated cells; cell multiplication and the effect of interferon on C-type oncornaviruses; and the effect of interferon on oncornaviruses other than the C-type. Some conclusions reached from these studies are as follows: the interferon-induced antiviral state primarily affects a post-transcriptional viral event resulting in the defective processing of viral RNA, C-type virus particles produced by interferon-treated cells have discrete alterations in the spectrum of their proteins and have a lower infectivity, and interferon does not affect the establishment of exogenous infections nor does it eradicate the virus from chronically infected cells. Interferon appears to only affect the expression of the incorporated proviral genome, and it can be speculated that interferon acts on the translation of several proteins that play a role in the processing of viral RNA or in the subsequent enveloping, or in both. Additional information on the effect of interferon on oncornaviruses other than the C-type indicates that intracisternal A-type particles occurring in interferon-sensitive mouse cell lines are resistant and that B-type mammary tumor virus produced by an interferon-sensitive cell line is only marginally affected. (26 Refs)

102. SYNTHESIS AND CLEAVAGE PROCESSING OF ONCORNAVIRUS PROTEINS DURING INTERFERON INHIBITION OF VIRUS PARTICLE RELEASE.
Shapiro SZ, Strand M, Billiau A
Dept. Molecular Biology, Albert Einstein Coll. Medicine, Bronx, NY 10461
Infect Immun; 16(3):742-747 1977

The effect of interferon on the rate of synthesis and the cleavage processing of viral proteins in mouse cells, chronically infected with Rauscher murine leukemia virus, has been studied by immunoprecipitation of newly synthesized viral proteins from virus-infected cells pulse-labeled with [S35]methionine. Immunoprecipitated, labeled polypeptides were resolved by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate and then examined by autoradiography. Cleavage processing was studied in the same manner with cells that had been pulse-labeled and then incubated with non-radioactive media for a sufficient time to allow normal cleavage processing to occur. At a concentration that strongly inhibited the release of virus particles, interferon had no effect on the synthesis of proteins carrying antigenic determinants of the major core protein p30 or of the envelope glycoprotein gp69/71. Nor did it affect the post-transitional cleavage processing of the precursors to these proteins. Similarly, interferon did not affect labeling or chasing of precursor protein carrying the p15 determinants; labeling of p15 itself could not be studied because it does not contain methionine. (Author abstract) (22 Refs)

103. TRAPPING OF ONCORNAVIRUS PARTICLES AT THE SURFACE OF INTERFERON-TREATED CELLS.
Billiau A, Heremans H, Allen PT, De Maeyer-Guignard J, De Somer P
Rega Inst., Div. Microbiology, Faculty Medicine, Univ. Leuven, B-3000 Leuven, Belgium
Virology; 73(2):548-552 1976

Interferon (Newcastle disease virus-induced mouse L-929 cell interferon) inhibited the release of C-type oncornaviruses in a Rauscher leukemia virus carrier cell line (JLSV5). At the same time particles accumulated at the outer cell surface, as determined by electron microscopy. These particles were counted in cell homogenates or in thin sections of cells. By using interferon at 30 to 3,000 reference units/ml, the increase averaged threefold for the cell homogenates and fivefold for the cell sections. Using mock interferon, interferon from different sources, and a highly purified preparation, it was determined that the virus-trapping effect observed was due to the interferon molecule rather than to some form of impurity in the experimental preparations. (16 Refs)

104. TRAPPING OF ONCORNAVIRUS PARTICLES AT THE SURFACE OF INTERFERON-TREATED CELLS.
Billiau A, Heremans H, Allen PT, De Maeyer-Guignard J, De Somer P
Rega Inst., Div. Microbiology, Faculty Medicine, Univ. Leuven, B-3000 Leuven, Belgium
Virology; 73(2):537-542 1976

The effects of interferon treatment on the release of C-type oncornaviruses were studied in a Rauscher leukemia virus carrier cell line (JLSV5) using crude Newcastle disease virus-induced mouse L-929 cell interferon. Treatment with 100 reference units/ml for 24 hr resulted in a 20-fold inhibition of C-virus release as measured by both reverse transcriptase and by electron microscope counting of particles.

Serum deprivation did not mimic this effect, and control experiments indicated that only active interferon preparations were effective. Electron microscope counting of a large number of cell sections confirmed the results from determinations on cell homogenates, since there were many more cells with many particles after treatment. The increase in the number of cell-associated virus particles averaged 3.5-fold in several experiments, and the av decrease in the number of particles released was 5-fold. The effects of interferon treatment on the number of particles in the budding stage was ambiguous, being significantly increased in 5 of 10 experiments. Possible mechanisms are discussed. (16 refs)

105. INFLUENCE OF INTERFERON ON THE SYNTHESIS OF VIRUS PARTICLES IN ONCORNAVIRUS CARRIER CELL LINES. IV. RELEVANCE TO THE POTENTIAL APPLICATION OF INTERFERON IN NATURAL INFECTIOUS DISEASES.

Billiau A, Heremans H, Allen PT, De Somer P
Div. Microbiology, Dept. Human Biology, Rega Inst., Univ. Leuven, Leuven, Belgium
J Infect Dis; 133(Suppl):A51-A55 1976

The effect of interferon on the release of Rauscher murine leukemia virus from chronically infected JLSV5 cells was determined by assaying radioactivity in the medium when virus particles had been labeled with 5'(3)H-uridine or 14C-amino acids, by assaying reverse transcriptase in the supernatant, and by direct quantitative electron microscopy counting. The dose response curves of the first three methods were superimposable, as was that of the inhibition of replication of exogenously added vesicular stomatitis virus. The inhibition of particle release measured by electron microscopy was less pronounced: pretreatment of cultures with 100 reference units of interferon/ml reduced the microscopic particle count 6-fold, compared to a 100-fold decrease as measured by reverse transcriptase activity or determination of radiolabeled virus. It is concluded that interferon inhibits the release of newly formed extracellular C-type virus, that the dose required is similar to that required for creation of the antiviral state as measured by infection with exogenous virus, and that cells pretreated with interferon continue to release a considerable number of particles that may contain a marked reduction of reverse transcriptase. Quantitative electron microscopic evaluation of cell-associated C-type virus indicated that interferon pretreatment caused an increase in the total number of C-type particles associated with the cells. The number of budding particles was not altered. In addition to a reduced transcriptase content, the newly formed virus particles made during interferon treatment may also lack proteins necessary for final release. It is suggested that, in vivo, interferon may be expected to reduce tissue damage due to antigen-antibody complex formation, but not damage due to cytolytic immune attack on cells carrying the antigen. (17 refs)

106. INFLUENCE OF INTERFERON ON VIRUS-PARTICLE SYNTHESIS IN ONCORNAVIRUS-CARRIER LINES. II. EVIDENCE FOR A DIRECT EFFECT ON PARTICLE RELEASE.

Billiau A, Edy VG, Sobis H, de Somer P
Dept. Microbiology, Rega Inst., Univ. Leuven, Belgium
Int J Cancer; 14(3):335-340 1974

Interferon treatment of murine C-type oncornavirus carrier lines (MO-P cells producing infectious Kirsten murine sarcoma virus and JLSV5 cells producing infectious Rauscher murine leukemia virus) results in a drastic inhibition of extracellular virus formation. When such cells were subcultured in the presence of interferon, synthesis of extracellular C-type virus remained depressed until the interferon treatment was discontinued. Cell-associated virus as seen in the electron microscope or as detected by uridine incorporation was not proportionally inhibited. The results suggest that interferon treatment primarily inhibits virus release.

107. THE SYNTHESIS AND PROCESSING OF STRUCTURAL PROTEINS OF RAUSCHER MURINE LEUKEMIA VIRUS.

Shapiro SZ
Yeshiva Univ., New York, NY 10033
Diss Abstr Int [B]; 37(5): 2081B 1976

The synthesis and post-translational processing of three structural proteins of Rauscher murine leukemia virus was examined by autoradiography of radiolabeled proteins. Polypeptides carrying virus specific antigenic determinants were immunoprecipitated with monospecific antiserum directed against either the Rauscher virus envelope glycoprotein gp69/71, the major core protein p30, or a small molecular wt internal protein p15. Analysis of polypeptides immunoprecipitated by anti-gp69/71 serum revealed a 90,000 dalton protein (Pr90) as the immediate precursor of gp69/71. Labeling with H3 sugars revealed that Pr90 was glycosylated but its carbohydrate moiety was deficient in fucose relative to the mature envelope protein. The synthesis of a 70,000 dalton polypeptide with gp69/71 antigenic determinants was observed when glycosylation was inhibited. Analysis of the polypeptides immunoprecipitated by anti-p30 serum and anti-p15 serum indicated that these virion proteins were both cleavage products of a 65,000 dalton precursor molecule (Pr65). Tryptic digest analysis showed that the 65,000-dalton molecules precipitated by each of these were identical and confirmed the precursor-product relationship of Pr65 to the virion protein p30. Pr65 was not detectable when viral specific protein was synthesized in the presence of amino acid analogs which can inhibit precursor protein cleavage. Released virions were found to contain Pr65 and intermediate sized cleavage products carrying antigenic determinants of virion proteins p30 and p15 in addition to the mature sized proteins. Precursor to gp69/71 was not detected in released virus particles. The effect of *interferon* on the rate of synthesis and the cleavage processing of viral proteins in mouse cells chronically infected with Rauscher murine leukemia virus was also studied. At a concentration that strongly inhibited the release of virus particles, interferon had no effect on the synthesis of proteins carrying antigenic determinants of gp69/71, p30 or p15 nor did it affect the post-translational cleavage processing of these proteins. Rauscher virions propagated in normal rat kidney (NRK) was infectious for two mouse cell lines (NIH/3T3 and III6A) and for Kirsten sarcoma virus transformed NRK cells but not for uninfected NRK cells. Rauscher virions grown in the three susceptible cell lines, however, were infectious for NRK cells. Upon examination of the envelope glycoproteins of virus propagated in NRK cells and III6A cells a post-release cleavage event was detected; this cleavage processing of the virus envelope protein did not appear to occur with the virus propagated in NRK cells. (0 Refs)

108. VIRUS-SPECIFIC RNA SYNTHESIS IN INTERFERON-TREATED MOUSE CELLS PRODUCTIVELY INFECTED WITH MOLONEY MURINE LEUKEMIA VIRUS.

Fan H, MacIsaac P
Tumor Virology Lab., Salk Inst., San Diego, CA, 92112
J Virol; 27(2):449-452 1978

NIH-3T3 mouse cells productively infected with Moloney murine leukemia virus (M-MuLV clone 1 cells) were treated with interferon (IF: 30 units for 16-24 hr), and intracellular virus-specific RNA was determined by hybridization with complementary DNA. The steady-state concentration of virus-specific RNA was 1.7 times greater in IF-treated cells than in untreated cells. This suggests that virus-specific RNA synthesis continues after IF treatment and that the increased level of virus-specific RNA may result from the failure of virus particles containing virion RNA to bud from the cell surface. This suggestion was tested by determining the rate of virus-specific RNA synthesis (ie, the hybridization of pulse-labeled nuclear RNA) in treated and untreated cells. The fraction of labeled virus-specific RNA was approx equal in both cell groups. Thus, virus-specific RNA synthesis continued at approx normal rates in IF treated mouse cells chronically infected with M-MuLV. The data support the conclusion that the primary site of the action of IF on MuLV producer cells is at virus assembly. (18 Refs)

109. LOCALIZATION OF REVERSE-TRANSCRIPTASE IN INTERFERON-TREATED MOUSE CELLS CHRONICALLY INFECTED WITH MOLONEY LEUKEMIA VIRUS.

Sherman L, Eylan E, Teitz Y
(c/o Teitz) Dept. Human Microbiology, Sackler Sch. Medicine, Tel-Aviv Univ., Tel-Aviv, Israel
Arch Virol; 66(2):143-155 1980

Interferon treatment of mouse cells chronically infected with Moloney leukemia virus (3T3/MLV) resulted in 97% inhibition of infective virus release. The intracellular localization and distribution of virus reverse-transcriptase and group specific (gs) antigen were determined in interferon treated and control cells. Cytoplasm of infected cells was fractionated by isopycnic centrifugation on discontinuous sucrose gradients. Fractions were analyzed for their chemical composition and characterized by the activity of membranal marker enzymes. The association and levels of viral antigens were determined in each fraction. Fractions enriched with 5' nucleotidase, specific enzyme marker for plasma membrane, were also enriched with viral proteins. In interferon treated cells, intracellular accumulation of viral proteins was specifically localized in the plasma membrane. Threefold increase in reverse-transcriptase level was the max accumulation found in purified plasma membranes. Intracellular enzyme levels in interferon treated cells were in accordance with the amount of cell associated infective virus particles. The small accumulation of viral proteins and infective virus particles was not sufficient to account for the great reduction in virus yield observed in the supernatants of the interferon treated cells. A possible role for interferon in modification of plasma membrane associated with virus assembly is postulated. (Author abstract) (35 Refs)

110. EFFECT OF INTERFERON ON REVERSE TRANSCRIPTASE BIOSYNTHESIS IN MOLONEY LEUKEMIA VIRUS INFECTION (MEETING ABSTRACT).

Sherman L, Eylan E, Teitz Y
Sackler Sch. Medicine, Tel Aviv Univ., Tel Aviv, Israel
Isr J Med Sci; 15(1):104 1979

The mode of action of interferon on the metabolic process involved in the morphogenesis of Moloney leukemia virus (MLV) was studied. The effect of interferon on the various stages of viral encapsidation process was investigated by examining virus and cell-associated reverse transcriptase activity. In an attempt to clarify the effect of interferon on enzyme protein synthesis and processing, the localization of viral-induced enzyme in the different cellular membranes of the infected cells was determined. Subcellular fractions were prepared from homogenized 3T3/NIH cell line chronically infected with MLV, analyzed for chemical composition and characterized by enzymatic markers. Interferon treatment of the cells resulted in a decrease of virus yield concomitant with an increase of intracellular viral antigens and reverse transcriptase activity. Maximal enzyme activity in interferon-treated cells was found 24 hr after treatment. Under these same conditions, enzyme accumulation up to 3 x more than control was associated with plasma membranes in which virus maturation and budding take place. These results suggest a late step of interferon effect on viral enzyme protein cleavage processing during the assembly of the virions. Characterization of enzyme precursors accumulated in the plasma membranes due to interferon treatment will be attempted. (no Refs)

111. EFFECT OF INTERFERON ON THE REPLICATION AND REVERSE TRANSCRIPTASE BIOSYNTHESIS OF MOLONEY LEUKEMIA VIRUS IN CHRONICALLY INFECTED CELLS (MEETING ABSTRACT).

Sherman L, Eylan E, Teitz Y
Sackler Sch. Medicine, Tel Aviv Univ., Tel Aviv, Israel
Isr J Med Sci; 14(7):820-821 1978

The mode of action of interferon on Moloney leukemia virus (MLV) in chronically infected mouse cells was studied by examining virus- and cell-associated reverse transcriptase activity. Interferon treatment of 3T3/NIH cell line, chronically infected with MLV, resulted in a temporal decrease of virus release. Under identical conditions, no suppression of intracellular levels of reverse transcriptase activity and virus complement fixation antigen were observed. On the contrary, higher levels of enzyme activity and complement fixation antigen were detected, suggesting accumulation of these proteins. Intracellular viral reverse transcriptase is easily quantitated since, in extranuclear fractions and cell extracts, this activity is far greater than that of normal cellular DNA polymerase. Optimal conditions for enzyme accumulation were examined. Max enzyme activity was found 24 hr after interferon treatment. Under these same conditions, enzyme accumulation in different subcellular fractions was compared. It was found that highest specific activity of the enzyme, up to three times more than control, was associated with plasma membranes in which virus assembly and budding took place. These results suggest a late interferon effect on viral enzyme protein cleavage processing or integration into the budding virion. An attempt to clarify the effect of interferon on enzyme protein processing was carried out by examining the electrophoretic mobility of enzyme activity on cellulose acetate (Cellogel). Differences in the mobility of enzyme activity might be due to interferon block in enzyme protein processing. (no Refs)

112. INTERACTION BETWEEN HUMAN INTERFERON AND HUMAN CELLS RELEASING ONCORNAVIRUSES (MEETING ABSTRACT).

Aboud M, Heller A, Salzberg S, Gurari-Rotman D, Revel M
Bar-Ilan Univ., Ramat Gan, Israel
Isr J Med Sci; 15(1):65 1979

Human RD-114 cells chronically infected with a feline RNA tumor virus were treated with different concentrations of human interferon (HIF) in order to determine the kinetics of development of the antiviral state in human cells. Virus release was monitored by reverse transcriptase activity in the culture medium. Likewise, the persistence of the antiviral state in human cells was determined after HIF removal. Our results demonstrated that within 3 hr after the addition of IF, 2.5 reverse transcriptase reduction dose 50% (RTRD50) units, there is 30% inhibition in virus release, and 65% inhibition at about 4 hr. Similarly, the antiviral state induced in RD-114 cells appeared to be rather stable since, even 24 hr after HIF removal, over 70% inhibition in virus release was observed in cells treated with IF, 2.5 RTRD50 units. HIF and mouse interferon showed species specificity when tested for their effects on virus release from RD-114 and mouse NIH/3T3 (murine leukemia virus) cells. Finally, HIF was titrated on RD-114 cells by either monitoring reverse transcriptase activity in the culture medium or determining the reduction in number of plaques formed on the cell monolayer after infection with vesicular stomatitis virus. Both assays were identical in their sensitivity. (no Refs)

113. EFFECT OF INTERFERON ON MOUSE CELLS CHRONICALLY INFECTED WITH MURINE LEUKAEMIA VIRUS: KINETIC STUDIES ON VIRUS PRODUCTION AND VIRUS RNA SYNTHESIS.

Salzberg S, Bakhanashvili M, Aboud M
Dept. Life Sciences, Bar-Han Univ., Ramat-Gan, Israel
J Gen Virol; 40(part1):121-130 1978

NIH/3T3 cells chronically infected with the Moloney strain of murine leukemia virus were incubated with interferon (IF). There was no effect on virus production during the first 4 hr, but thereafter an antiviral state gradually developed, reaching a max at about 12 hr. When IF was removed, the antiviral state (expressed in terms of inhibition of release of virus) remained constant for 10 hr, after which there was an abrupt return to the normal rate of virus release. Analysis of IF-treated cells showed that there was a three to fourfold increase in the amount of virus RNA in the nucleus at 48 hr after IF addition, and still a slight increase at 72 hr. There were no increases in the amounts of virus RNA in the cytoplasm 72 hr after the addition of IF. These results agree with the postulate that IF *inhibits a late stage in the maturation of virus in chronically infected cells.* (Author abstract) (22 Refs)

114. FRIEND VIRUS-SPECIFIC RNAS IN FRIEND ERYTHROLEUKEMIC CELLS TREATED WITH INTERFERON (MEETING ABSTRACT).

Dolei A, Capobianchi MR, Colletta G, Ferrentino M, Rossi GB, Vecchio G
Istituto di Virologia, Universita di Roma, Rome, Italy
Abstracts of the 12th Meeting of the European Tumor Virus Group, held in Belgium, September 10-14, 1979, 1979.

The effects of interferon (IF) on friend leukemia cells (FLC) were analyzed with respect to the expression of the friend virus complex (FLV), composed by the lymphatic leukemia (LLV) and the spleen focus forming (SFFV) viruses. IF almost completely blocks the release of viral particles but does not inhibit viral protein synthesis. Cr0t values from hybridization of FLC RNAs with a LLV-specific cDNA probe show that in IF-treated FLC the levels of LLV-specific cytoplasmic RNAs are decreased in the log phase of cell growth, as compared to untreated FLC; later, the levels of LLV-specific RNAs reached the control values. The accumulation in the nucleus seems to be similar in IF-treated and control FLC, thus suggesting that the IF-sensitive step is either the turnover or the rate of synthesis and the migration of LLV-specific RNAs to the cytoplasm. Parallel analyses with two cDNA probes, one specific for LLV and the other specific for both LLV and SFFV, are in progress and will allow evaluation of the differential expression of the two genomes. This is being performed in cells maintained in the exponential phase of growth, in which condition virus release in control cells is max and the effects of IF are more evident. (no Refs)

115. INTERFERON AND FRIEND LEUKEMIA CELLS IN CULTURE.

Rossi GB, Dolei A, Cioe L, Benedetto A, Matarese GP, Belardelli F, Rita G
Sezione di Virologia, Instituto Superiore di Sanita, Rome e Cattedra di Patologia Generale, Universita di Camerino, Camerino, Italy
Tex Rep Biol Med; 35:420-428 1977

Experiments on the effect of interferon on Friend leukemia cells (FLC) in culture are reported. Experiments with unstimulated FLC in culture showed that interferon inhibits cell growth in a dose-dependent fashion. Furthermore, the inhibition is fully reversible and is not apparently mediated by a toxic effect. Autoradiographic studies indicated that the action of interferon is mediated by a block in the early G2 phase of the cell cycle. In experiments with dimethyl sulfoxide-stimulated FLC, interferon administration significantly decreased globin messenger RNA accumulation and almost completely blocked beta and alpha chain synthesis, suggesting that interferon administration to FLC, while inhibiting the release of Friend leukemia virus mature virions, did not impair the production of at least some viral antigens. Although the mechanism of interferon action is not fully understood, it seems virtually certain that the crucial interaction takes place at the cell surface. (14 Refs)

116. PRODUCTION OF FRIEND LEUKAEMIA ANTIGENS IN CHRONICALLY-INFECTED CELLS TREATED WITH INTERFERON.

Ramoni C, Rossi GB, Matarese GP
Lab. Cell Biology and Immunology, Istituto Superiore di Sanita, Rome, Italy
J Gen Virol; 37(2):285-296 1977

The effect of mouse interferon (ITF) on the expression of Friend leukaemia virus (FLV) and on dimethyl sulfoxide (DMSO)-stimulated Hb synthesis in Friend erythroleukemic cells (FLC) was studied. Immunofluorescent staining was used to detect intracellular antigens, and incorporation of labeled H3-uridine into virions to detect extracellular virus release. Interferon markedly inhibited Hb synthesis and FLV production, but enhanced accumulation of virus antigens in the cytoplasm; on the cell surface, however, FLV antigens were present to the same extent whether ITF was present or not. When ITF was removed, virus production rose and intracellular virus antigens fell to the levels of untreated controls. (Author abstract) (39 Refs)

117. ENHANCED EXPRESSION OF FRIEND LEUKEMIA VIRUS ANTIGENS IN CARRIER CELL LINES TREATED WITH INTERFERON.

Ramoni C, Rossi GB, Grappelli C
Labs of Physics and Microbiology, Istituto Superiore di Sanita, 00161 Rome, Italy
Proc Am Assoc Cancer Res; 17:215 1976

This study was designed to determine whether interferon (IF) treatment of Friend Leukemia Virus (FLV)-induced carrier cell lines would affect the synthesis of FLV antigens under conditions where the production of FLV virions is inhibited by IF. Evidence for this was given by the markedly decreased release of radio-labelled 1.16 g/ml particles in the supernatant of cultures treated with IF and then labelled with H-uridine. Infectivity of such culture supernatants was also reduced. However, IF -treated cells, stained by indirect immunofluorescence with an FLV-neutralizing antiserum, showed unreduced or enhanced amounts of FLV antigens, the addition of dimethyl sulfoxide to the culture medium being irrelevant. This evidence, as well as that from Billiau et al and Friedman et al (Personal Communications, August 1975) suggests that IF acts either at a late stage in FLV replication or during FLV release. (Author Abstract)

118. INCREASE IN INTRACISTERNAL A-TYPE PARTICLES IN FRIEND CELLS DURING INHIBITION OF FRIEND VIRUS (SFFV) RELEASE BY INTERFERON OR AZIDOTHYMIDINE.

Krieg CJ, Ostertag W, Clauss U, Pragnell IB, Swetly P, Roesler G, Weimann BJ
Max-Planck-Institut fur Experimentelle Medizin, D-3400 Gottingen, Germany
Exp Cell Res; 116(1):21-29 1978

The effects of interferon and azidothymidine (N3T), which are known inhibitors of Friend virus synthesis, on the levels of intracisternal A-type particles in Friend erythroleukemic (F4-6) cells were studied. Treatment with interferon (300 IU/ml for 4 days) or N3T (0.25 mM for 35 hr) inhibited spleen focus-forming virus (SFFV) production, reverse transcriptase activity, and the number of C-type particles while increasing the number of intracisternal A-type particles per cell 1-to 20-fold. The A-type particles released from the treated cells did not differ in ultrastructure from those released from untreated cells. Interferon treatment of B8 cells, which show an a priori low level of C-type virus synthesis, did not result in an increase in A-type particles. Similarly, the number of A-type particles was not increased by interferon treatment of three C-type virus-releasing cell lines, although C-type virus release was inhibited. Viral RNA levels were not markedly increased during inhibition of C-type virus release in F4-6 cells. The presence and accumulation of A-type particles seems to be related to the production of Friend virus complex (SFFV). (41 Refs)

119. EFFECT OF INTERFERON ON DIMETHYL SULFOXIDE-STIMULATED FRIEND ERYTHROLEUKEMIC CELLS: ULTRASTRUCTURAL AND BIOCHEMICAL STUDY.

Luftig RB, Conscience JF, Skoultchi A, McMillan P, Revel M, Ruddle FH
Worcester Foundation for Experimental Biology, Shrewsburg, MA 01545
J Virol; 23(3):799-810 1977

The mechanism of interferon action on dimethyl sulfoxide (DMSO)-stimulated Friend erythroleukemic cells from clone 745 was investigated. Fifty U of mouse interferon in 1.5% DMSO were added to the cells on day 1. After 6 days of this treatment, the minimal effect on growth rate suggested that this quantity of interferon was well below that needed to produce a decrease in proliferative response. Interferon did, however, produce a small, significant increase in Hb production. Interferon effected a rapid decrease in the total number of newly synthesized virus particles in the cells; there was also a parallel decrease in the number of cell sections exhibiting virions. Accumulation of extracellular virus ceased by 5 to 10 hr after treatment. After interferon addition, there was an increase in the number of enveloped A-type particles. These results suggest an inhibition of a late stage of virus maturation as well as inhibition of virus release. There was also an increase in the av number of empty shell particles 12 to 16 hr after treatment; these could represent incomplete products of virus assembly. Cytoplasmic vacuole structures (CVS) decreased in parallel with the total virion production. It is suggested that interferon treatment results in a decrease in the surface area available for viral production and thus in a decrease in virus transport. This is coupled with a defect in maturation leading to more immature forms. There appears to be a decreased synthesis of a viral protein needed in the CVS membrane for virus assembly. (29 Refs)

120. THE INFLUENCE OF EXOGENOUS INTERFERON ON THE COURSE OF LATENT ONCORNAVIRUS INFECTION OF J-96 CELLS.

Solov'ev VD, Kishchak VIa, Bektemirov TA, Bocharov AF, Moisiadi SA, Delimbetova GA, Chuev IuV
Central Inst. Postgraduate Medical Studies, Moscow, USSR
Vopr Virusol; (2):196-202 1977

The effect of exogenous WBC interferon (10 units/ml) was investigated in chronic oncornavirus infection of lymphoblastoid J-96 cells producing type B virus. After 18 to 34 passages, virion formation was inhibited 2.0- to 4.4-fold and virus budding was inhibited 1.6- to 2.7-fold. There was no inhibiting effect on the formation of intracytoplasmic type A virions. The oncornavirus that was produced retained its biological activity in KC cells. Electrophoresis of the cell membranes showed an accumulation of 115,000, 100,000 and 68,000 mol wt glycoproteins in the cell fraction. The cells were also found to have two- to three-fold increases in the inter-species group-specific antigen of Mason-Pfizer virus. The mechanism of action of interferon is discussed. (20 Refs)

121. INCREASE IN RETROVIRUS PRODUCTION BY AN ANTI-INTERFERON SERUM (MEETING ABSTRACT).

Lidereau R, Sinoussi F, Montagnier L, Chermann JC
Unite d'Oncologie Virale, Institut Pasteur, Paris, France
Bull Cancer (Paris); 66(3):296 1979

The addition of interferon to infected cells causes an inhibition of retrovirus production in a late stage (assembly or budding) of replication. It was shown that the endogenous interferon plays an important role in viral replication. Addition of anti-interferon serum to cells chronically infected with Moloney leukemogenic virus results in a sharp increase of viral production (measured by reverse transcriptase activity). This effect is totally neutralized by the addition of excess interferon. During iododeoxyuridine induction, a 50-fold increase of endogenous viruses in K-Balb/c cells is observed in the presence of anti-interferon anti-serum. One of the controls of endogenous virus expression must be associated with the interferon. (no Refs)

II. SENSITIVITY/ RESISTANCE STUDIES OF INTERFERONS' ANTIVIRAL ACTIVITY

A.

Factors Influencing Sensitivity/Resistance of Viruses to Interferons

122. DIFFERENTIAL EFFICACIES OF HUMAN TYPE I AND TYPE II INTERFERONS AS ANTIVIRAL AND ANTIPROLIFERATIVE AGENTS.

Rubin BY, Gupta SL
Interferon Lab., Sloan-Kettering Inst. Cancer Res., New York, NY, 10021
Proc Natl Acad Sci USA; 77(10,part2):5928-5932 1980

Treatment of human fibroblast FS-4 cultures with human type II interferon preparations induced the synthesis of at least four proteins that were similar in size to four of the five proteins induced by type I interferons (Mr 120,000, 88,000, 67,000, and 56,000). However, the Mr 67,000 and 56,000 proteins were induced more strongly by type II than by type I interferon, and a counterpart of a Mr 80,000 protein induced by type I interferons was not noticeably induced by type II interferon preparations. We therefore compared type I and type II interferons for relative antiviral activities against different viruses (vesicular stomatitis, encephalomyocarditis, vaccinia viruses and reovirus) and for cell growth-inhibitory activities on various cell types. The replication of vesicular stomatitis and encephalomyocarditis viruses was inhibited more strongly by type I interferon, whereas reovirus and vaccinia virus showed greater sensitivity to type II interferon preparations. This indicates that viruses may differ in their sensitivity to human type I and type II interferons and that the antiviral mechanisms induced by type I and type II interferons may have significant differences. The type I and type II interferons may also differ in their efficacies as antiproliferative agents. Type II interferon preparations at 2.5 units/ml inhibited the incorporation of [3H]thymidine to a greater extent than did type I interferon at 400 units/ml. (For both type I and type II interferons, the unit of interferon activity was defined as the concentration that decreased the yield of vesicular stomatitis virus by 50% in FS-4 cultures.) Furthermore, whereas type II interferon preparations had a reversible cytostatic effect on normal human fibroblasts at 10 units/ml, the transformed cells tested (HeLa, osteosarcoma, U-amnion) showed extensive cell death, thus indicating that they may have a cytocidal effect on certain tumor cells. It appears that human type II interferon (or a factor present in these preparations) may be a potent antitumor agent. (Author abstract) (38 Refs)

123. INFLUENCE OF INPUT MULTIPLICITY OF INFECTION ON THE ANTIVIRAL ACTIVITY OF INTERFERON.

Stitz L, Schellekens H
Virology Section, Primate Center TNO, P. O. Box 5815, 2280 HV Rijswijk, Netherlands
J Gen Virol; 46(1):205-210 1980

The antiviral activity of interferon was shown to be dependent on the input multiplicity of infection (moi). Cells could not be protected against the cytopathogenic effect of vaccinia, herpes, Echo or vesicular stomatitis virus at moi greater than 1. At a moi of less than or equal to 1, cells could be protected but the amount of interferon necessary to yield protection was inversely related to the moi. When protection was afforded, it was only transient. The duration of the antiviral effect of interferon was also inversely related to the moi. The dependence of the antiviral effect on the moi could not be explained by assuming the viruses to be mixtures of subtypes with different interferon sensitivity. Also, selection by interferon treatment of interferon-insensitive subtypes could not be shown. The greater antiviral effect of interferon at low moi was probably not caused by induction of interferon by the infecting virus. A direct inactivation by the virus of the antiviral effect of interferon could not be demonstrated. These results indicate than when interferon-treated cells are infected, they will not survive the infection. The only result of the interferon treatment will be to inhibit virus replication to some extent, leading only to a delay in cell death. (Author abstract) (22 Refs)

124. HETEROGENEITY OF THE SENSITIVITY OF VESICULAR STOMATITIS VIRUS TO INTERFERONS.

Ito Y, Montagnier L
Germfree Life Res. Inst., Nagoya Univ. Sch. Medicine, Showa-ku, Nagoya, Japan
Infect Immun; 18(1):23-27 1977

Twelve cloned viruses were randomly isolated from original (uncloned) vesicular stomatitis virus (VSV), and their sensitivities to mouse and human interferons were examined. When the interferon sensitivities of these various VSVs were compared by the plaque reduction method in L cells, virus 3 was found to be sevenfold more sensitive than virus 11, and the interferon sensitivity of the original (uncloned) virus was intermediate. The present study shows that uncloned VSV Indiana strain is a mixture of viruses that have different sensitivities to interferon. The slope of the dose-response curve of original (uncloned) virus to mouse interferon was less steep than those of cloned viruses. Virus 11, which was the least sensitive to mouse interferon, was relatively sensitive to human interferon. There was no correlation between the sensitivities of virus clones to mouse interferon and their sensitivities to human interferon. When the interferon sensitivities were tested by various assay methods (plaque reduction, yield reduction, and cytopathic effect inhibition), the ranking of the interferon sensitivities of different viruses was not changed. These results indicate that the relative sensitivity of a virus to interferon is determined by the host cells in which the tests are performed, but not by assay method used. (Author abstract) (11 Refs)

125. PROTECTION OF MICE AGAINST INFECTION WITH WILD-TYPE MENGO VIRUS AND AN INTERFERON SENSITIVE MUTANT (IS-1) BY POLYNUCLEOTIDES AND INTERFERONS.

Stebbing N
Searle Res. Lab., Lane End Road, High Wycombe, Bucks, England
J Gen Virol; 44(1):255-260 1979

Single-stranded polynucleotide preparations [transfer RNA, polyriboinosinic acid (poly-rI) plus poly-5-hydroxycytidylic acid (poly-ho5C)-copolymer] which protect mice against picornavirus infections without inducing interferon, protected mice equally against infection with an interferon-sensitive mutant (IS-i) of Mengo virus and with wild-type virus (IS+). Poly(rI)-poly(rC) and mouse macrophage interferon [ie serum from mice treated with poly(rI)-poly(rC)] protected mice equally against infections with the two viruses, but fibroblast interferon protected better against infection with the interferon-sensitive mutant than with the wild-type

virus. These and other results indicate that: Mengo virus has a genetic locus affecting sensitivity to fibroblast but not macrophage interferon; these two types of interferon have different mechanisms of action against Mengo virus infections in mice; Mengo virus genes controlling sensitivity to fibroblast interferon may modulate disease since infection in vivo induces only fibroblast interferon; the antiviral activity of the single-stranded polynucleotides is unlikely to be mediated by induction of either macrophage or fibroblast interferon. (Author abstract) (11 Refs)

126. DISSOCIATION OF INTERFERON EFFECTS ON MURINE LEUKEMIA VIRUS AND ENCEPHALOMYOCARDITIS VIRUS REPLICATION IN MOUSE CELLS.

Czarniecki CW, Sreevalsan T, Friedman RM, Panet A
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, Bethesda, MD, 20205
J Virol; 37(2):827-831 1981

Two subclones of Swiss mouse cells infected with Moloney murine leukemia virus (M-MuLV) were tested for their response to interferon (IFN). Whereas M-MuLV production in the two subclones was inhibited to the same extent, one of the subclones was significantly more sensitive to IFN when the antiviral effect was measured by replication of encephalomyocarditis (EMC) virus. The same subclone was also more sensitive to the anticellular activities of IFN. Additionally, NIH 3T3 cells infected with M-MuLV were completely resistant to IFN actions when EMC virus replication or the anticellular activities were tested. However, under the same conditions, M-MuLV production was completely inhibited by IFN. These results indicate that IFN may affect cell growth functions and EMC replication through mechanisms different from those by which MuLV production is inhibited. (Author abstract) (14 Refs)

127. RESISTANCE OF VISNA VIRUS TO INTERFERON.

Carroll D, Ventura P, Haase A, Rinaldo CR, Overall JC, Glasgow LA
Univ. California Service, Veterans Admin. Hosp., 151F, Building 1, Room 10, 4150 Clement St., San Francisco, CA, 94121
J Infect Dis; 138(5):614-617 1978

The effect of interferon on the replication of visna virus was investigated. Sheep choroid plexus cells were incubated overnight with fetal lamb interferon and challenged with visna virus. No significant inhibition of plaque formation by visna virus occurred. Interferon did not affect the kinetics of viral production nor the final yield of virus in a single cycle of growth. The addition of interferon at later times in the viral life cycle did not inhibit production of visna virus. Cells pretreated with interferon do not become resistant to infection with visna virus. (11 Refs)

128. VIRAL RESISTANCE TO INTERFERON.

Metz DH, Douglas AR
Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England
Tex Rep Biol Med; 35:260-263 1977

A method to select for interferon-resistant virus mutants is described. An attempt to obtain mutants of the encephalomyocarditis (EMC) virus using this technique are reported. EMC virus was first treated with or grown in the presence of a mutagen (5-fluoro-deoxyuridine, nitrous acid, proflavine, or N-methyl-N-nitro-N-nitrosoguanidine) at a dose sufficient to reduce the virus titer by a factor of 10**-2 to 10**-3. Stocks of mutated virus were titrated on monolayers of L cells treated with 25 reference units/ml mouse interferon. Plaques were picked after 3 days incubation at 37 C and re-inoculated onto L cell monolayers treated with 25 units/ml interferon. If a full viral cytopathic effect (cpe: approx 40% of plaques originally picked) developed, a sample of the medium was passed into another culture with 25 units/ml interferon. Samples of medium from those cultures showing a cpe were titrated in the absence of interferon, incubated for 3 days, and representative plaques inoculated into L cells. Interferon sensitivity of these stocks and of wild-type stocks were measured by observing cpe in serial dilutions or by a plaque reduction assay. Of 430 EMC plaques picked at the first stage, none showed reduced interferon sensitivity at the final stage. The same results were obtained with 40 plaques picked after treatment with 250 units/ml interferon. This failure to select mutants with enhanced interferon resistance is discussed in terms of the possible mechanisms of action of interferon, and in terms of possible therapeutic uses of interferon. (9 Refs)

129. DIFFERENTIAL SENSITIVITY OF RAUSCHER MURINE LEUKAEMIA VIRUS (MULV-R) TO INTERFERONS IN TWO INTERFERON-RESPONSIVE CELL LINES.

Allen PT, Schellekens H, Van Griensven LJ, Billiau A
Rega Inst., Div. Microbiology, Faculty Medicine, Univ. Leuven, B-3000 Leuven, Belgium
J Gen Virol; 31(3):429-435 1976

The effect of interferon on the replication of vesicular stomatitis virus (VSV) and type C oncornavirus in two Balb/c mouse cell lines, (JLS-V5 and JLS-V9R) infected with MuLV-R was examined. A microtiter procedure or a dye uptake method was used to determine interferon concentrations. VSV replication was inhibited threefold in both cell lines by 10 to 20 units of interferon/ml. In JLS-V5 cells type C virus yields, as measured by H-uridine incorporation and reverse transcriptase activity, were also reduced threefold by 10 to 20 units of interferon/ml. However, in JLS-V9R cells, type C virus replication was refractory to interferon at concentrations up to 1 x 10 units/ml. Infectious type virus transmitted from JLS-V9R cells to Balb/3T3 cells was as sensitive to interferon as virus transmitted from JLS-V5 cells, indicating that resistance of type C virus in JLS-V9R cells is a feature of the cells rather than of the virus strain. (19 refs)

130. INFLUENCE OF INTERFERON ON VIRUS PARTICLE FORMATION IN DIFFERENT ONCORNAVIRUS CARRIER CELL LINES.

Billiau A, Sobis H, de Somer P
Rega Inst., U. Leuven, Belgium
Int J Cancer; 12(3):646-653 1973

The short-term effect of mouse interferon and viral functions in the following cell lines was studied: cells producing infectious C-type particles, either Kirsten MSV in MO-P cells, or Rauscher-MLV in JLSV5 cells; S+L- cells carrying Moloney-MSV in a rescuable form and releasing noninfectious C-type particles; and MO4 cells carrying Kirsten-MSV in a rescuable form and producing intracisternal, noninfectious A-type particles. In the infectious virus-producing lines (MO-P and JLSV5), interferon caused a dose-dependent decrease in virus production as measured by the uridine incorporation technique. In S+L- cells, the uridine incorporation profile was not altered by exposure to interferon, although these results do not indicate whether the replication of the S+L- virus occurs through an interferon-sensitive mechanism. The MO4 cells displayed normal sensitivity to interferon when monitored by a vesicular stomatitis virus (VSV) challenge. Exposure to interferon did not prevent the increase in the type-A particle count induced by sequential exposure to bromodeoxyuridine and dimethylsulfoxide.

Thus, the noninfectious A-type particles are synthesized by a different mechanism than that by which infectious C-type viruses are made, in that they escape the antiviral action of exogenous interferon.

131. RESPONSE OF CLONED PROGENY OF CLINICAL ISOLATES OF HERPES SIMPLEX VIRUS TO HUMAN LEUKOCYTE INTERFERON.

Lazar R, Breinig MK, Armstrong JA, Ho M
Dept. Microbiology, Graduate Sch. Public Health, Univ. Pittsburgh, Pittsburgh, PA, 15261
Infect Immun; 28(3):708-712 1980

First- and third-generation cloned progeny viruses were derived from clinical isolates of herpes simplex virus and examined for their sensitivities to human interferon by inhibition of plaque formation in Vero cells. The dose-response curves obtained with the first- and third-generation clones were similar to those obtained with the parental isolates, and both the parent and the clones showed similar sensitivities to interferon. These results suggest that clinical isolates of Herpes simplex virus consist of a homogeneous population of virus particles with respect to interferon sensitivity. The dose-response curves obtained with herpes simplex virus demonstratcd a shallower slope than those obtained with vesicular stomatitis virus. Vesicular stomatitis virus plaque formation was completely inhibited at high concentrations of interferon, whereas complete inhibition of plaque formation by Herpes simplex virus did not occur at the highest concentration of interferon used. Cloned progeny were derived from plaques appearing in the presence of high concentrations of interferon. The dose-response curves and interferon sensitivities of these clones were similar to those of the parent and third-generation clone from which they were derived. There was no evidence for genetic heterogeneity with respect to interferon sensitivity. (Author abstract) (14 Refs)

132. SENSITIVITY OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 TO THREE PREPARATIONS OF HUMAN INTERFERON.

Overall JC, Yeh TJ, Kern ER
Dept. Pediatrics, Howard Hughes Medical Inst. Lab., Salt Lake City, UT
J Infect Dis; 142(6):943 1980

Ten isolates of herpes simplex virus (HSV) type 1 and 9 isolates of HSV type 2 were tested against virus-induced (alpha), fibroblast (beta), and mitogen-induced (gamma) preparations of human interferon (HuIFN). HSV type 2 was slightly more sensitive and HSV type 1 somewhat less sensitive to all three preparations of HuIFN than Sindbis and vesicular stomatitis virus - both considered to be quite sensitive to HuIFN. HSV type 2 was significantly more sensitive than HSV type 1 to each of the HuIFN preparations (p less than 0.01; Mann-Whitney rank-sum test). Clinical isolates did not appear to differ from laboratory strains. These results indicate that both HSV types 1 and 2 are sensitive to the three different preparations of HuIFN. HuIFN may have a role in natural recovery from and may have potential as an antiviral chemotherapeutic agent in HSV infections in humans. (Author abstract) (no Refs)

133. COMPARATIVE STUDY OF THE SENSITIVITY OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 TO HUMAN LEUKOCYTE INTERFERON IN VITRO.

Matsubara M, Imanishi J, Yasuno H, Kagami K, Ozaki Y, Pak CB, Kishida T
Dept. Dermatology, Kyoto Prefectual Univ. Medicine, Kawaramachi Hirokoji, Kamikyoku, Kyoto, 602, Japan
J Dermatol (Tokyo); 7(3):203-206 1980

The sensitivity of herpes simplex virus (HSV) to human leukocyte interferon (HL-IF) was investigated in cultures of human embryonic fibroblasts (HEF). Nine HSV strains (5, Type 1; 3, Type 2) were isolated from patients and in HEF cultures that had been pretreated with 1 x 10(4) IU of HL-IF for 24 hr. Two or 3 days after the HSV inoculation, cytopathic effect or giant cell formation was observed, and the median tissue culture infective dose was calculated. The HL-IF was observed to protect the HEF for 2 and 3 days from infection by eight of the nine strains of HSV; one of the Type 2 strains showed lower protection on day 3. Statistical studies showed, however, that there was no significant difference in the HL-IF sensitivities of Type 1 HSV and Type 2 HSV or in the sensitivities of the various strains within each type. (16 Refs)

134. CONTROL OF SIMIAN VIRUS 40 GENE EXPRESSION IN ADENOVIRUS-SIMIAN VIRUS 40 HYBRID VIRUSES: SYNTHESIS OF HYBRID ADENOVIRUS 2-SIMIAN VIRUS 40 RNA MOLECULES IN CELLS INFECTED WITH A NONDEFECTIVE ADENOVIRUS 2-SIMIAN VIRUS 40 HYBRID VIRUS.

Oxman MN, Levin MJ, Lewis AM
Virus Res. Unit, Children's Hosp. Med. Ctr., Boston, Mass.
J Virol; 13(2):322-330 1974

The effect of interferon on simian virus 40 (SV40) and adenovirus 2 (Ad2) T antigen synthesis was examined in African green monkey kidney cells infected with SV40, Ad2, or a nondefective Ad2-SV40 hybrid virus (Ad2+ND4). The induction of SV40 T antigen by SV40 was highly sensitive to interferon, whereas the induction of Ad2 T antigen by Ad2 was resistant. This difference in interferon sensitivity was also noted in cells simultaneously infected with both viruses. However, the induction of SV40 T antigen by Ad2+ND4, which contains covalently linked SV40 and Ad2 DNAs, was as resistant to interferon as was the induction of Ad2 T antigen. This change in the interferon sensitivity of SV40 T antigen synthesis suggests that the expression of at least this portion of the SV40 genetic information in Ad2+ND4 is under Ad2 genetic control. When RNA extracted from Ad2+ND4-infected cells was examined by means of sequential hybridization with Ad2 DNA, elution, and rehybridization with SV40 DNA, 27% was detected in control mixtures of Ad2 and SV40 RNAs. The presence of Ad2 and SV40 nucleotide sequences in the same RNA molecule indicates that, in Ad2+ND4 infection, transcription is initiated in the DNA of one virus (Ad2 or SV40) and continues without interruption across the point of junction into the DNA of the other virus. Furthermore, the interferon resistance of Ad2+ND4-induced SV40 T antigen synthesis suggests that transcription of the genetic information for SV40 T antigen is initiated in a region of Ad2 DNA.

B.

Transfer of Interferon-induced Viral Resistance

135. TRANSFER OF INTERFERON-INDUCED VIRAL RESISTANCE FROM HUMAN LEUKOCYTES TO OTHER CELL TYPES.
Blalock JE, Weigent DA, Langford MP, Stanton GJ
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Infect Immun; 29(2):356-360 1980

Nonsensitized human leukocytes cocultured with various xenogeneic epithelioid and fibroblastic cells produced human leukocyte interferon and shortly thereafter transferred antiviral activity to the xenogeneic cells. Antiviral activity in the cocultured xenogeneic cells was not due to cell-mediated cytotoxicity as measured by specific 51Cr release and staining with vital dyes. The transfer of antiviral activity from leukocytes to xenogeneic cells was blocked by rabbit antiserum to human leukocyte interferon. Transferred viral resistance failed to develop in actinomycin D-treated xenogeneic cells, even though these cells induced human leukocyte interferon. Based on these findings, it appears that interferon made in the cocultures acts on the leukocytes to effect the transfer of interferon-induced viral resistance to the xenogeneic cells, possibly by transmission of an inducer for the antiviral state. These studies strongly suggest a new and efficient host defense against virus infection which does not require killing of noninfected or recently infected cells. (Author abstract) (12 Refs)

136. HUMAN LYMPHOCYTE TRANSFER OF VIRAL RESISTANCE (MEETING ABSTRACT).
Stanton GJ, Weigent DA, Langford MP, Blalock JE
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
J Clin Hematol Oncol; 9(4):280 1979

Nonsensitized human lymphocytes cocultured with various species of heterologous or transformed cells produce human WBC interferon (IF) and transfer antiviral activity (AA) to the foreign cell. 103.5 units/ml IF and 99% reduction in sindbis virus yields were detected when 5-10:1 lymphocytes to recipient cells were co-cultivated for 24 hr. Antiviral activity in recipient cells was detectable at 4 hr and max at 8 hr. Cytotoxicity in cell cultures measured during this time by 51Cr release, neutral red uptake and trypan blue dye exclusion could not account for the decrease in virus produced. Human IF concentrations at 4 and 8 hr were 10 and 100 units, respectively, and no antiviral activity directed against nonhuman cells was detected in supernates. The results suggest that transfer of AA was efficient and rapid, required presence of foreign cells, occurred in presence of human IF, and did not appear to result from cytotoxicity. (no Refs)

137. EFFICIENT TRANSFER OF INTERFERON-INDUCED VIRUS RESISTANCE BETWEEN HUMAN CELLS.
Blalock JE, Stanton GJ
Dept. Microbiology, Univ. Texas, Medical Branch, Galveston, TX, 77550
J Gen Virol; 41(2):325-331 1978

The rate of development of interferon-induced virus resistance in a mixture of two human cell types (U and WISH) is determined by the cell type (WISH) in the mixture which responds first. This phenomenon has been shown with two types of interferon assay procedure, and with both vesicular stomatitis virus and Sindbis virus. The transfer of virus resistance from one human cell (WISH) to another (U) (homospecific transfer) is much more efficient than the transfer from mouse L cells to WISH cells (heterospecific transfer), as shown by a much lower ratio of donor to recipient cells required for max transfer as well as a more rapid transfer. Thus, virus protection afforded by the interferon system is amplified more efficiently in mixtures of different human cells than in mixtures of mouse and human cells. These results suggest that, in a mixed population of cells such as occurs in vivo, more slowly responding cells might be influenced by cells which respond more rapidly to interferon. A defensive role is suggested for this mechanism which amplifies protection due to interferon. (Author abstract) (9 Refs)

138. INTERFERON INDUCED TRANSFER OF VIRAL RESISTANCE: POSSIBLE NATURAL FUNCTIONS AND IMPLICATIONS (MEETING ABSTRACT).
Blalock JE
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
J Clin Hematol Oncol; 9(4):280 1979

Interferon-induced transfer of viral resistance between heterologous cells was previously demonstrated. This process has now been shown to occur within a single cell line. Cloned L cells were shown to be very heterogeneous in their time and dose responses to mouse interferon. Sensitive cells transferred interferon-induced viral resistance to less sensitive cells making them almost equally sensitive. A small fraction of cells was found to determine the overall response of the 'parental' L cell population. Based on these findings a new mechanism of interferon action on cells not in direct contact with interferon was proposed. The implications of this proposal to polypeptide hormone action are currently under study and will be discussed. (no Refs)

139. MECHANISMS OF INTERFERON INDUCED TRANSFER OF VIRAL RESISTANCE BETWEEN ANIMAL CELLS.
Blalock JE, Baron S
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
J Gen Virol; 42(2):363-372 1979

The sequence of events initiated by interferon and leading to the antiviral state were studied as possible sites for the cell-to-cell transfer of interferon induced viral resistance. The possible role of interferon produced by recipient cells was negated by the demonstration of transfer of resistance in the presence of anti-human interferon antibody and under conditions of a single cycle of vesicular stomatitis virus growth. Transfer of sensitivity of human amnion cells to mouse interferon, possibly through transfer of a membrane receptor, seems unlikely since resistance was transferred in the absence of mouse interferon. From kinetic data and the fact that actinomycin D blocked resistance in human cells for 3 hr longer than in mouse cells, it seems unlikely that the mouse antiviral protein itself or its messenger RNA alone is a likely candidate for the transfer of resistance. Thus, by a process of elimination, we suggest that secondary messenger molecules which transmit the interferon signal from the membrane to the nucleus are the effector substance(s) for the transfer process. (Author abstract) (28 Refs)

140. INTERFERON-INDUCED TRANSFER OF VIRAL RESISTANCE BETWEEN ANIMAL CELLS.
Blalock JE, Baron S
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX 77550
Nature (Lond); 269(5627):422-425 1977

The ability of interferon-treated mouse L cells to transfer their antiviral resistance to cocultivated heterologous cells is examined. Mouse L cells were incubated at various concen-

trations in the presence of either human (WISH) cells or baby hamster kidney (BHK) cells in the presence or absence of mouse C243 cell interferon. WISH and BHK cells alone are insensitive to the action of mouse interferon. Cocultivation of WISH cells in the presence of mouse interferon and sensitive L cells resulted in significant inhibition of the expected viral yield from the WISH cells. Partially purified L-cell interferon caused the same transfer of inhibition in a 1:1 mixture of L and WISH cells. Incubation of L and WISH cells in the presence of 2 microg/ml actinomycin D blocked both the action of mouse interferon on the L cells and the resistance transfer to the WISH cells. Transfer of viral resistance seemed to be a function of interferon itself, which once transferred had the characteristics of the interferon-induced antiviral state. The transferred resistance seemed to occur between several different species of cells and was dependent upon the ratio of homologous to heterologous cells as well as absolute cell density at the given ratio. (19 Refs)

141. THE TRANSFER OF INTERFERON-INDUCED VIRAL RESISTANCE BETWEEN ANIMAL CELLS.

Blalock JE, Baron S
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Tex Rep Biol Med; 35:307-315 1977

In summary we have shown that interferon treated mouse L cells can transfer their antiviral resistance to cocultured heterologous (human WISH or baby hamster kidney) cells which are insensitive to mouse interferon. Transfer of viral resistance seems to be initiated by interferon itself. Once transferred the viral resistance has the characteristics of the interferon-induced antiviral state. The transferred resistance occurs between several cell species. The transfer of resistance depends on the ratio of cells homologous (to interferon) to cells which are heterologous as well as to the absolute cell density at a given ratio. The transfer process is efficient in that it requires relatively small amounts of interferon. Finally, we propose that this phenomenon is a natural process for amplification of the interferon system and preliminary evidence indicates that it occurs by cell to cell transfer of an interferon-induced molecule. (Author abstract) (20 Refs)

C.
Cellular Factors Influencing Sensitivity/ Resistance to Interferons' Antiviral Action

1.
Cytogenetic Factors Influencing Sensitivity to the Interferon-induced Antiviral State

142. THE ROLE OF HUMAN CHROMOSOME 21 IN SENSITIVITY TO INTERFERONS.

Wiranowska-Stewart M, Stewart WE
Interferon Lab., Sloan-Kettering Inst. Cancer Res., New York, NY 10021
J Gen Virol; 37(3):629-633 1977

Cultures of human fibroblasts trisomic for chromosome 21 were more sensitive to human WBC and human fibroblast interferons than were human diploid fibroblasts; these in turn were more sensitive than fibroblasts monosomic for chromosome 21. The sensitivities of these cells to human interferons correlated with the amounts of interferons which they bound. These data indicate that some gene on chromosome 21 codes for an interferon-receptor component. Also, interferon from a heterologous species (mouse) was respectively much more and somewhat more active in trisomic and disomic cells than in monosomic cells. These data suggest that heterologous and homologous interferons may share common receptor component(s) coded by chromosome 21. Alternatively, human chromosome 21 may carry genetic information for some factor(s) responsible for increasing the exposure of certain surface receptors which are themselves coded by other chromosomes. (Author abstract) (23 Refs)

143. CYTOGENETIC ANALYSIS OF THE SENSITIVITY TO ANTI-VIRAL AND ANTI-CELL GROWTH ACTIVITIES OF HUMAN FIBROBLAST INTERFERON IN ANEUPLOID HUMAN TUMOR CELL LINES.

Lubiniecki AS, Jones V, Eatherly C
Life Sciences Div., Meloy Lab., Inc., 6715 Electronics Drive, Springfield, VA, 22151
Arch Virol; 60(3/4):341-346 1979

The ability of human fibroblast interferon to suppress colony formation and papovavirus T-antigen expression in six human tumor cell lines did not appear to correlate with their content of chromosomes 16 and 21. Additional factors or chromosomes may be involved in the manifestation of interferon action in aneuploid cells. (Author abstract) (17 Refs)

144. INTERFERON EFFECT ON RIBOSOMAL RIBONUCLEIC ACID RELATED TO CHROMOSOME 21 PLOIDY.

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Dept. Medical Sciences, Southern Illinois Univ. Sch. Medicine, P. O. Box 3926, Springfield, IL, 62708
Biochem J; 179(1):221-225 1979

Antiviral and cell-growth-inhibitory activities of human interferon were shown to be related to the activity of a gene or genes present on chromosome 21. The 18 Svedberg (S) ribosomal RNA (rRNA) is vital to cell growth; it is capable of a viral-messenger RNA-recognition function and it is coded for by genes a portion of which are present on chromosome 21. A previously reported ability of human interferon to affect rRNA metabolism is characterized by a decrease in the sucrose-gradient-peak ratio of radiolabeled 28S to 18S rRNA in extracts from the cytoplasm of interferon-treated human fibroblasts. In the present report, interferon dose-response curves are presented demonstrating a direct relationship between a decrease in this ratio and interferon concentrations in the media. By using this virus-independent cytoplasmic rRNA assay, eight human fibroblast lines, differing in chromosome 21 ploidy, were tested for sensitivity to human interferon. Two monosomy-21, two euploid-21 and four trisomy-21 cell lines were tested. The monosomy-21 cell populations were significantly less sensitive to interferon than the other six cell types tested. Of the cell lines tested, the most sensitive, by a wide margin, was a trisomy-21 line. Trisomy-21 cell monolayer sensitivity, however, varied widely within the range from normal to supersensitive. These observations suggest that the ability of interferon to affect rRNA metabolism is related to the activity of a gene or genes present on chromosome 21. (Author abstract) (18 Refs)

145. SENSITIVITY OF HUMAN-MOUSE SOMATIC CELL HYBRIDS TO HUMAN INTERFERON.

Slate DL, Ruddle FH
Dept. Human Genetics and Biology, Yale Univ., New Haven, CT
Cytogenet Cell Genet; 22(1-6):270-274 1978

The sensitivity of human-mouse somatic cell hybrids to human interferon was examined. A series of human-mouse somatic cell hybrids with only human chromosome 21 and

with one or two additional human chromosomes were evaluated for their differential sensitivity to human leukocyte and fibroblast interferons. Three subclones of WAV hybrids, derived from a fusion of mouse A9 cells with the diploid human fibroblast WI38, were studied by karyotypic and isozyme analysis. Results demonstrated that human chromosome 21 alone is sufficient for sensitivity to human interferon. Extracts of WAVR4d-F9-4a treated with human interferon exhibit phosphoprotein patterns similar to those of mouse interferon-treated L cells. The WAV series provides a system for studying the putative human-specific interferon receptor and the influence of other chromosomes on the cell membrane. Experiments with antisera to each of these lines may help to determine the number of receptors on normal human and hybrid cells, and the kinetics of attaining the antiviral state. (10 Refs)

146. THE SOMATIC CELL GENETICS OF THE INTERFERON SYSTEM (MEETING ABSTRACT).

Ruddle FH, Slate DL
Dept. Biology, Yale Univ., New Haven, CT, 06520
Fed Proc; 38(3,part1):777 1979

Somatic cell genetics provides a direct approach to the genetic analysis of in vitro cell populations. Parasexual events such as gene transfer and gene loss can be used to elucidate the genetic organization of mammalian cells, making it possible to map genes to chromosomes and to regions of chromosomes. More than 200 genes have been mapped in man by this method. The interferon system is well suited to such analysis. It has been possible to show that interferon production and sensitivity are separate genetic functions mediated by genes on separate chromosomes. Sensitivity to human interferon is controlled by a gene or genes located on chromosome 21. Immunochemical evidence suggests that this gene(s) specifies a cell surface receptor, specific for the human form of interferon. Chromosome 21 alone is sufficient for the expression of the human interferon receptor. The production of human interferon is coded by genes on other chromosomes. Genes which code for the human fibroblast form of interferon reside on chromosomes 2 and 5. The emerging picture based on cell genetics and immunochemistry is one of multiple structural genes specifying a family of different human interferons. The interferon system grows in complexity, and it is likely that many genes control its function - a great many of these genes are certain to be amenable to somatic cell genetic analysis. (no Refs)

147. ANTIBODIES TO CHROMOSOME 21 CODED CELL SURFACE COMPONENTS CAN BLOCK RESPONSE TO HUMAN INTERFERON.

Slate DL, Ruddle FH
Dept. Human Genetics and Biology, Yale Univ., New Haven, CT
Cytogenet Cell Genet; 22(1-6):265-269 1978

Antibodies to chromosome 21 coded cell surface components which can block response to human interferon were studied. The laboratory produced antisera to a number of human-mouse somatic cell hybrids, including one which has chromosome 21 as its only detectable human genetic material. Blocking activity could be found in antiserum raised against the chromosome 21-only cell line, and the line could effectively be used to remove such activity when used for preadsorption. Cells were injected into mice to elicit antibody production in the following combinations: A9, no human chromosomes present; WAVR4d with human chromosomes 4, 21, 22 present; WAVR4d-A19 with human chromosomes 21, 22 present; WAVR4d-F9-4a with human chromosome 21 present. Treatment with antisera raised against any of the WAV lines shifted the dose-response curve to the right, indicating increased virus yields. Non-preadsorbed anti-A9 serum had a small blocking effect which may have been due to similarities in surface components involved in interferon binding between mouse and human cells. Preadsorption of antiserum on WAVR4d-F9-4a removed most of the blocking activity originally present in the antiserum. The WAVR4d-A19 and WAVR4d lines were also effective in this respect, whereas preadsorption onto a hybrid not containing chromosome 21 did not alter blocking activity. The finding that antiserum can be raised against a hybrid containing only human chromosome 21 makes possible the use of this serum as a probe for the putative interferon receptor. (8 Refs)

148. HUMAN CHROMOSOME 21 DOSAGE: EFFECT ON THE EXPRESSION OF THE INTERFERON INDUCED ANTIVIRAL STATE.

Tan YH, Schneider EL, Tischfield J, Epstein CJ, Ruddle FH
Kline Biol. Tower, Yale U., New Haven, Conn.
Science; 186(4158):61-63 1974

Fibroblast cultures were established from skin biopsies of patients with Down's syndrome and from their normal siblings. To quantitatively assess the antiviral state induced by interferon in human trisomic 21 (T-21) and normal diploid (D-21) cells, five matched pairs of fibroblast cultures were exposed for 20-24 hr to different concentrations of human leukocyte interferon. The cells were subsequently challenged with vesicular stomatitis virus (VSV) and examined 36-48 hr later for virus-induced cytopathogenic effects (CPE). The concentrations of human interferon required to inhibit viral replication by 50% were 3-7 times higher for the D-21 than for the T-21 cells. The T-21 cells were more sensitive than the D-21 cells to the action of interferon; this effect was specific for trisomy of chromosome 21 since the concentration required to induce an antiviral state in T-18 and T-13 fibroblasts was the same as required for protection of D-21 fibroblasts. The T-21 cells were also 3-7 times more sensitive than the D-21 cells to the antiviral action of poly (I).poly(C); this was not due to a nonspecific increase in interferon induction. The data suggest that the extra chromosome 21 in T-21 cells is responsible for the enhancement of protection by interferon, which is consistent with the assignment of the gene for the expression of the antiviral state to chromosome 21.

149. CHROMOSOME-21-DOSAGE EFFECT ON INDUCIBILITY OF ANTI-VIRAL GENE(S).

Tan YH
Baltimore City Hosp., Baltimore, MD 21224
Nature (Lond); 253(5489):280-282 1975

A new approach to assess the presence of a regulatory gene function which modulates the expression of the structural gene for the anti-viral state (AVS) is reported. AVS was induced in monosomic, disomic and trisomic human fibroblast cultures by exposing them to various concentrations of human interferon. It was found that the logarithm of inducibility of the AVS in human cells increases linearly with the number of human chromosomes 21 present. Extrapolation of this relationship to zero chromosome 21 suggests that a cell cannot be induced by AVS if chromosome 21 is absent. The logarithmic increase shows that complex mechanisms, presumably regulatory in function, are involved. It is possible that cellular regulation by interchromosomal gene interaction is responsible for human disorders associated with the loss or gain of a single chromosome.

150. STUDY OF RELATIONSHIP BETWEEN INTERFERON-INDUCED ANTIVIRUS STATE AND CHROMOSOME COMPLEMENT OF CULTURED HUMAN CELLS.

Solov'ev VD, Khesin IE, Gulevich NE, Amchenkova AM, Narovlianskii AN, Stonova NS, Podkidysheva LN, Grinberg KN, Kukharenko VI

N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR

Dokl Akad Nauk SSSR; 243(4):1069-1071 1978

The role of chromosome complement in the expression of interferon-induced antivirus state was studied in four cultures of human cells (stable heteroploid line J-96, its subline J-41, continuous line 375 that was derived from a skin biopsy of a child with Down's syndrome, and a control diploid fibroblast culture). The cultures were incubated with human leukocytic interferon (3,600 IU/ml) and infected with vesicular stomatitis virus. The av number of chromosome 21 per complement in cells J-96, J-41, 375, and control cells was 1.57, 0.26, 3.0 and 2.0, respectively (the av number of chromosome 16 was 2.6, 2.7, 2.0, and 2.0, respectively). The av interferon dose required to produce an antivirus state in 2 x 10(5) cells infected with virus at 100 TCD50 was 112.0 IU for J-96, 1,800 IU for J-41, 0.9 IU for 375, and 14.9 IU for control diploid cells. These findings confirm the role of chromosome 21 in the expression of an antivirus state and do not contradict literature data suggesting that chromosome 16 is the possible location of the repressor gene. (8 Refs)

2.
Species Specificity and Other Cellular Factors Influencing Sensitivity to the Interferon-induced Antiviral State

151. COMPARISON OF THE SUPPRESSION OF CELL AND VIRUS GROWTH IN TRANSFORMED HUMAN CELLS BY LEUKOCYTE AND FIBROBLAST INTERFERON.

Kuwata T, Fuse A, Suzuki N, Morinaga N

Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan

J Gen Virol; 43(2):435-439 1979

The effects of human WBC interferon (L-IF) and fibroblast interferon (F-IF) on the growth of the transformed human cell lines RSa and RSb were compared. Each of these cell lines was considerably more sensitive to F-IF than to L-IF. Cells of an IFr line (which was isolated from the RSa line) were fairly resistant to 1,000-20,000 units/ml of L-IF, but their growth was suppressed by continued treatment with 1,000-2,000 units/ml of F-IF. Cells of another resistant line (F-IFr) derived from the RSa line were only partially resistant to F-IF and were more resistant to L-IF. The antiviral actions of L-IF and F-IF in RSa, RSb, and IFr cells also were compared. With all three lines, the amounts of vesicular stomatitis virus formed in a yield-reduction test were decreased to about 0.1% of the control value when the cells were treated with 10 units of either L-IF or F-IF and to 0.01% of the control value when the cells were treated with 100 units of L-IF or F-IF. Thus, there were no significant differences in the antiviral actions of L-IF and F-IF. (24 Refs)

152. INITIAL INTERACTION OF HUMAN FIBROBLAST AND LEUKOCYTE INTERFERONS WITH FS-4 FIBROBLASTS.

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Dept. Microbiology, New York Univ. Sch. Medicine, New York, NY, 10016

J Gen Virol; 44(1):161-168 1979

Human FS-(4) cells were exposed to human fibroblast interferon for various times and futher incubated in the absence of interferon until challenged with vesicular stomatitis virus. Addition of antibody to fibroblast interferon at the time of removal of interferon did not alter the development of the antiviral state. If cells were exposed to interferon for 45 min at either 0 or 37 C, they developed resistance upon subsequent incubation at 37 C. However, less resistance developed if the cells were initially incubated at 0 C. Our results indicate that a single interaction of fibroblast interferon with susceptible cells, either at 0 or 37 C, is sufficient for the subsequent development of an antiviral state, at least in the short term experiment. The kinetics of development of the antiviral state were compared with fibroblast and WBC interferon. The rise in the degree of antiviral resistance was steeper and max levels of resistance were reached sooner when FS-(4) cells were incubated with increasing concentrations of fibroblast interferon than with WBC interferon. This suggests a greater affinity of fibroblast interferon for these cells. (Author abstract) (16 Refs)

153. IMMUNE AND VIRUS-INDUCED INTERFERONS MAY ACTIVATE CELLS BY DIFFERENT DEREPRESSIONAL MECHANISMS.

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Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550

Nature (Lond); 283(5745):400-402 1980

Differences in the kinetics of induction of the antiviral state by immune interferon (IIF) and virus-induced interferon (VIF) activated cells were investigated. Cultures of murine L cells or human WISH or foreskin cells were treated with cycloheximide, followed by either IIF or VIF; the cells were then washed and challenged with either GD-7 virus (murine cells) or Sindbis (human cells) virus. VIF-treated cells developed antiviral activity, whereas IIF-treated cells did not. Further experiments in which cells were pretreated with both actinomycin D and cycloheximide suggested that IIF does not directly induce a messenger RNA for antiviral or effector protein(s), but that VIF does. The results show that the different kinetics of induction of the antiviral state by the two types of interferon result from a major difference in the mechanism by which IIF and VIF activate cells. (11 Refs)

154. MOUSE FIBROBLAST (TYPE I) AND IMMUNE (TYPE II) INTERFERONS: PRONOUNCED DIFFERENCES IN AFFINITY FOR GANGLIOSIDES AND IN ANTIVIRAL AND ANTIGROWTH EFFECTS ON MOUSE LEUKEMIA L-1210R CELLS.

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Dept. Biochemistry, Medical Coll. Wisconsin, Milwaukee, WI, 53226

Proc Natl Acad Sci USA; 77(5):2528-2532 1980

Different interferons can be obtained from the same animal species depending on the cells and (or) the inducers use. Interferons of type I and type II differ not only antigenically but also in mol wt and stability at low pH. We have investigated whether mouse type I and type II interferons also differ in properties relating to their biological action. We present evidence which suggests that the molecular mecha-

nism leading to antiviral and antigrowth effects induced by both types of interferon in susceptible cells must differ in at least one important step. Antiviral and antigrowth activities of type I but not of type II interferon are both inhibited when gangliosides are added to cell cultures together with the interferon. Whereas type I interferon strongly binds to ganglioside affinity columns and can be eluted with solutions of N-acetylneuraminyllactose, type II interferon passes through such columns unretarded. L-1210 mouse leukemia cells (L-1210S) respond equally well to antiviral and antigrowth activities of type I and type II interferons. Type I and interferon-resistant L-1210 cells, derived from L-1210S cells after continuous culture in the presence of mouse fibroblast interferon, lack antiviral and antigrowth response to mouse type I interferon However, these cells display the same sensitivity toward type II interferon as do the parent L-1210S cells from which they were derived and respond equally well to its antiviral and antigrowth activities. (Author abstract) (29 Refs)

155. TYPE I AND TYPE II INTERFERONS: DIFFERENTIAL ANTIVIRAL ACTIONS IN TRANSFORMED CELLS.

Bourgeade MF, Chany C, Merigan TC
Institut National de la Sante et de la Recherche Medicale U.43, Hopital St. Vincent-de-Paul, 74 avenue Denfert-Rochereau, Paris 75014, France
J Gen Virol; 46(2):449-454 1980

In transformed mouse embryo cells, type II interferon had much less antiviral activity than type I interferon. In non-transformed cells, the two interferons had similar high activity. Reversal of the phenotype of Moloney sarcoma virus (MSV) transformed cells by sodium butyrate restored their sensitivity to the antiviral action of type II interferon. Additional evidence for a role of the cytoskeletal network in the action of type II interferon is that its antiviral effect is reduced by cytochalasin B, colchicine or vinblastine. MSV-transformed cells, selected for their resistance to the antiviral action of type I interferon, were sensitive to type II interferon. These differences in the effects of type I and II interferon on transformed cells are at present unexplained, but suggest that they have at least partially separate mechanisms of action. (Author abstract) (15 Refs)

156. ADSORPTION OF INTERFERON TO HOMOLOGOUS AND HETEROLOGOUS CELLS.

Degre M
Kapt. W. Wilhelmsen og Frues Bakteriologiske Institutt, Univ. Oslo, Rikshospitalet, Oslo, Norway
Arch Virol; 65(1):71-76 1980

Mouse and human interferons adsorbed well both to human and mouse cells. There was no difference in the recovery of homologous and heterologous interferons from the cells. Pretreatment of the cells with heterologous interferon did not prevent adsorption of subsequently applied homologous interferon and did not interfere with the antiviral activity of homologous interferon. (Author abstract) (18 Refs)

157. NEUTRALIZATION OF INTERFERON ACTIVITY IN HOMOLOGOUS AND HETEROLOGOUS CELLS WITH HOMOLOGOUS AND HETEROLOGOUS ANTIBODY.

Braude IA, De Clercq E, Zhen-Xi Z, Edy VG, De Somer P
Meloy Lab., Inc., Springfield, VA, 22151
Proc Soc Exp Biol Med; 165(1):161-166 1980

Human fibroblast interferon (IF) protected mouse L-929 cells against vesicular stomatitis virus infection, although it was about 20x less active than human WBC IF and 1,200x less active than mouse L-929 cell IF. Studies on the preparations on homologous and heterologous cells by homologous and heterologous antibody showed that IF-cell interactions were stronger for homologous than for heterologous combinations. Based on these findings, a model that considers only one IF within a given species was proposed. In this model, the active sites of different species are similar, and the degree of cell protection conveyed is dependent on the physicochemical fit between IF and cell receptor. By this arrangement, the receptor, in concert with some amplification and/or activator system, modulates the cells' response to IF. The closer the fit, the greater the signal conveyed and the greater the protection conferred. This model also applies for cell hybrids that contain the receptor of one species but the antiviral machinery of another. (33 Refs)

158. ESTABLISHMENT AND MAINTENANCE OF THE ANTI-VIRAL STATE IN THE PRESENCE OF A HETEROSPECIFIC NUCLEUS (MEETING ABSTRACT).

Veomett MJ, Veomett GE
Sch. Life Sciences, Univ. Nebraska, Lincoln, NB
J Cell Biol; 79(2,part2):403a 1978

Interferons are generally considered to be species specific; ie, interferons produced by cells of one species can induce an anti-viral state (AVS) in cells from that species but generally cannot induce an AVS in cells of other species. Interferons induce the AVS through cell-surface interactions that are presumed to be specific. We have examined the ability of heterokaryons formed from mouse (L) and human (HeLa) cells to enter the AVS in response to human and/or mouse interferon (IF) and have also examined the effects of a heterospecific nucleus on establishment or maintenance of the AVS. Heterokaryons or cybrids (whole cell x enucleated cell) were formed from L and HeLa cells or cytoplasts by fusion with Sendai virus and treated with human and/or mouse IF. After 18 to 24 hr, they were challenged with vaccinia virus, pulse labeled with 3H-thymidine, and then the number of infected cells determined by autoradiography. Similar experiments were performed with one component (either whole cell or cytoplast) of the fusion mixture already in the AVS. From these studies we conclude that (1) the AVS is dominant in heterokaryons, (2) the cytoplasm can confer the AVS on a whole cell, (3) a heterospecific nucleus interferes with the establishment of the AVS in heterokaryons, and (4) treatment of cybrids with IF homologous to the cell type of the enucleated parent does not elicit the AVS from the heterospecific nucleus. (no Refs)

159. INTERFERON AND ADRENOCORTICOTROPIC HORMONE INDUCTION OF STEROIDOGENESIS, MELANOGENESIS AND ANTIVIRAL ACTIVITY.

Blalock JE, Harp C
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Arch Virol; 67(1):45-49 1981

ACTH and mouse but not human interferon caused a steroidogenic response and induced antiviral activity in mouse adrenal tumor (Y-1) cells. ACTH and human but not mouse interferon caused induction of melanin synthesis and antiviral activity in human melanoma cells. ACTH did not induce antiviral activity in mouse L or human amnion (WISH) cells. The hormonal activities of interferon were neutralized by specific rabbit anti-interferon sera. Thus, interferon has species-specific hormonal activity and ACTH has cell-specific antiviral activity. These results are discussed in terms of the possible natural functions of interferon and polypeptide hormones. (Author abstract) (12 Refs)

160. MECHANISMS OF CROSS-SPECIES ACTIVITY OF MAMMALIAN INTERFERONS.

Carter WA
Dept. Medical Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Pharmacol Ther (Chemother); 7(2):245-252 1979

The glycoprotein interferon antiproliferative, antiviral, and immunomodulating activities were discussed. Cross-species antiviral and lectin-binding properties of WBC- and fibroblast-derived interferons were reviewed. Bioactivity of animal WBC interferon in human cells, and important factors for species specificity were discussed. Glycosylation effects on the interferon molecule, on hydrophobic molecular shape alterations, and implications for surface receptor acceptance and for secretion were surveyed. Chemical alteration of interferon to modify species-specificity and the use of animal-derived interferon in human systems were reported. (40 Refs)

161. BYPASSING THE 'SPECIES BARRIER' WITH CARBOHYDRATE-ALTERED INTERFERON FROM LEUKOCYTES.

Carter WA
Dept. Medical Viral Oncology, Roswell Park Memorial Inst. and State Univ. New York at Buffalo, Buffalo, NY, 14263
Cancer Res; 39(9):3796-3798 1979

Interferon, a glycoprotein with demonstrated antitumor and antiviral properties, can be obtained from cells of different species, and some of these interferons can be effective across species lines. I hypothesize that the ability to cross or not to cross species lines lies in the carbohydrate moiety, and cross-species biological activity is a property of the polypeptide. This would represent one of the first major roles uncovered for glycosylation in any biological system. If this hypothesis is correct, then it should be possible to use animal-derived interferon as a large scale, inexpensive source to treat human diseases. (Author abstract) (36 Refs)

162. BY-PASSING THE SPECIES BARRIER: ANIMAL LEUKOCYTE INTERFERONS AND HUMAN CELLS (MEETING ABSTRACT).

Carter WA
Roswell Park Memorial Inst., Buffalo, NY, 14263
J Clin Hematol Oncol; 9(4):269 1979

It has been recently shown that leukocyte interferon (IF) derived from bovine, porcine and equine sources protects human cells from viral challenge. Such IFs demonstrate a cross-species activity 3-10 fold greater than that observed in homologous cells. Lectin-binding studies reveal that major subcomponents of these IFs have altered glycosylation patterns similar to that of human leukocyte IF which protects cells of lower animals. In contrast, IFs derived from various fibroblast strains (human and non-human) show generally a 1,000-fold less activity on heterologous cells. Fibroblast IFs from various species are extensively glycosylated with abundant core and peripheral sugar groups. Apparently, extensive glycosylation of the IF polypeptide results in surface exposure of hydrophobic amino acids (? tyrosine) located within the bioactive site. D-mannose residues may also contribute to the increased hydrophobicity of fibroblast-derived IFs. (1 Ref)

163. MECHANISM OF INTERFERON ACTION. SPECIES SPECIFICITY OF INTERFERON AND OF THE INTERFERON-MEDIATED INHIBITOR OF TRANSLATION FROM MOUSE, MONKEY, AND HUMAN CELLS.

Samuel CE, Farris DA
Section Biochemistry and Molecular Biology, Dept. Biological Sciences, Univ. California, Santa Barbara, CA 93106
Virology; 77(2):556-565 1977

The species specificity of interferon and the interferon-mediated ribosome-associated inhibitor of translation from mouse fibroblast, African green monkey kidney, and human amnion cells was investigated. The antiviral activity of the above interferons was max on the homologous species of cells; however, significant cross-species activity was observed in the case of monkey and human cell:interferon combinations. For both monkey and human interferons, the titer determined on the heterologous cell species was about 60 +- 10% of the titer determined on the homologous cell species. Ribosomal salt-wash (potassium chloride) fractions prepared from interferon-treated mouse fibroblast, monkey kidney, and human amnion cells inhibited the translation of reovirus messenger RNA catalyzed by the mouse ascites cell-free protein synthesizing system prepared from untreated ascites cells. The apparent affinity with which the inhibitory factors present in interferon-treated cells were associated with ribosomes differed for different cell lines. Interferon-mediated factors could be released from ribosomes of human amnion and African green monkey kidney cells with buffer containing 0.12 M potassium chloride, whereas a concentration of 0.3 M was required to dissociate the inhibitory factor from ribosomes of mouse fibroblast cells. Interferon-mediated ribosome associated antiviral factor(s) does not appear to be species specific, even though certain interferons are relatively species specific. (37 Refs)

164. ANTIVIRAL ACTIVITY OF BOVINE INTERFERONS ON PRIMATE CELLS.

Tovey MG, Bandu MT, Begon-Lours J, Brouty-Boye D, Gresser I
Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94800 Villejuif, France
J Gen Virol; 36(2):341-344 1977

Potent preparations of bovine WBC and fibroblast interferons had substantial antiviral activity on monkey cells and low activity on human cells. Thus, interferon from a 'lower' phylogenetic species can have considerable antiviral activity in primate cells, but not all primate cells are equally sensitive. (Author abstract) (15 Refs)

165. EFFECT OF GLYCOLIPIDS DETECTABLE IN TRANSFORMED HUMAN CELLS ON INTERFERON ACTIVITIES.

Kuwata T, Handa S, Fuse A, Morinaga N
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
Biochem Biophys Res Commun; 85(1):77-84 1978

The glycolipid composition of the transformed human cell lines RSa, RSb, and IFr was analyzed and the interaction of the glycolipids and human interferon on these cells was investigated. All of the cell lines contained glucosylceramide, trihexosylceramide, globoside, GM3 and GM2. Pretreatment with GM3 or GM2 neutralized the antiviral action of human interferon. These glycolipids, therefore, are components of the receptor for interferon in these cells. Lactosylceramide also neutralized the antiviral action of interferon, but not as effectively as GM3 or GM2. Neither GM3 nor the ganglioside mixture had an inhibitory effect on the growth suppressive activity of interferon. (27 Refs)

166. EFFECTS OF INTERFERON ON CELL AND VIRUS GROWTH IN TRANSFORMED HUMAN CELL LINES.
Kuwata T, Fuse A, Morinaga N
Dept. Microbiology, Sch. Medicine, Chiba Univ. Chiba 280, Japan
J Gen Virol; 33(1):7-15 1976

The anticellular and antiviral effects of human interferon under different conditions were investigated in two clonal cell lines, RSa and RSb, from human embryonic cells transformed by Rous sarcoma virus and simian virus 40. Growth of RSb cells was reduced in proportion to the concentration of interferon, and many cells died with interferon treatment over 500 units/ml. Normal embryonic cells were less susceptible and were not killed by interferon treatment. In testing cultures of different cell density, interferon suppressed growth in RSb cultures with 10(6) cells, and also led to cell death in cultures of 2 x 10(5) cells; the effect of interferon on cell growth is thus more pronounced at low cell concentrations. In cultures of RSb cells treated with interferon (500 units/ml) for only 3 days and then washed, the cells first decreased in numbers and then recovered; cells treated with 1,000 units/ml for 3 days did not recover. A few RSb cells that survived treatment with 1,000 units/ml of interferon were then grown on interferon-free medium and found to be as interferon-sensitive as the parent RSb cells. When *interferon-resistant* cells (IFr), derived from RSa cells, were not treated with interferon, vesicular stomatitis virus (VSV) could multiply as well in IFr cells as in RSa cells. IFr cells were thus apparently resistant to the anticellular but not the antiviral activity of human interferon. About 1.28% to 2.50% of the total number of interferon units applied was recovered from RSa and RSb cells, whereas only 0.1% or less was recovered from IFr cells. In addition to the role of the number of binding sites on the cells, some regulatory system in RSa and RSb cells may exist that controls their sensitivity to interferon. (23 refs)

167. MEMBRANE RECEPTORS FOR INTERFERON.
Besancon F, Ankel H
Institut National de la Sante et de la Recherche Medicale, Hopital Saint Vincent de Paul, 74 avenue Denfert-Rochereau, 75014 Paris, France
Tex Rep Biol Med; 35:282-292 1977

Specific cell membrane receptors for interferon have been postulated based on a variety of different observations, such as the following: trypsin treatment of monkey-mouse hybrid cells preferentially destroys sensitivity to primate interferon; syngeneic mice immunized with human-mouse hybrid cells develop surface-directed antibodies, which only block antiviral action of human interferon; interferon covalently bound to Sepharose beads retains its antiviral activity despite the fact that diameters of the beads are several times those of the cells; cells challenged with poly I:C to produce interferon do not develop resistance to viral infection in the presence of interferon antiserum. Interferon has a strong and specific affinity for the carbohydrate side chain of cell membrane gangliosides. Preincubation of Sepharose-bound interferon with gangliosides inhibits antiviral activity in the following order of potency: GM2 greater than or equal to GM1 greater than or equal to GD1a. Derivatives of GM2 lacking either terminal N-acetyl-galactosamine or terminal N-acetyl-neuraminic acid are not (or very slightly) inhibitory; in addition, binding to gangliosides is reversed by N-acetyl-neuraminyl-lactose, the trisaccharide common to all gangliosides. These data clearly demonstrate interferon's specificity for the carbohydrate moiety of the ganglioside molecule. Phaeseolus vulgaris lectin, which blocks antiviral action of interferon, also prevents binding of interferon to ganglioside-Sepharose affinity columns. Many substances of known affinity for gangliosides likewise inhibit action of interferon. These include cholera and tetanus toxins, thyrotropin and human chorionic gonadotropin. Although a more general effect on the state of the membrane or on cellular metabolism by these substances cannot be ruled out, competition for interferon binding sites appears to be the most plausible explanation. Increased sensitivity of certain transformed cells to interferon upon uptake of exogenous gangliosides not only supports the concept that these glycolipids are involved in binding of interferon to the membrane, but furthermore points to the importance of interferon-ganglioside interaction for triggering of the antiviral response. (Author abstract) (30 Refs)

168. INTERFERON ACTION: ROLE OF MEMBRANE GANGLIOSIDES.
Vengris VE, Reynolds FH, Hollenberg MD, Pitha PM
Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205
Virology; 72(2):486-493 1976

The relationship between gangliosides and interferon action in normal human fibroblasts and in ganglioside-deficient transformed mouse embryo fibroblasts was studied. The antiviral activity of human (fibroblast + WBC) and mouse fibroblast interferon was neutralized by preincubation with ganglioside before application to cells. Ganglioside mixtures were as effective as pure gangliosides, with no particular ganglioside specificity observed for neutralization of human interferon. Ganglioside-agarose derivatives removed human interferon from soln; interferon was eluted with buffers containing urea, sodium dodecyl sulfate, and mercaptoethanol. Ganglioside-deficient transformed mouse cell lines were relatively insensitive to interferon action. Treatment of such cells with ganglioside led to an increase in membrane ganglioside content and in two of three cell lines to an increase in cell sensitivity to mouse interferon; in mouse SVS AL/N and TAL/N cells, GM2, GT1, and a mixture of crude gangliosides were effective, whereas GM1 and GD1a were without effect. The interferon sensitivity of untransformed cells, which failed to take up appreciable ganglioside, was not increased by treatment with exogenous ganglioside; the sensitivity of one GM1 -deficient transformed cell line (K-Balb/C-3T3) was not increased by pretreatment with ganglioside. These results indicate an interaction between gangliosides and several types of interferon and suggest a role for membrane gangliosides in the antiviral action of interferon. (29 refs)

169. THE ROLE OF CELL MEMBRANE IN THE ANTIVIRAL EFFECT OF INTERFERON.
Pitha PM, Vengris VE, Reynolds FH
Johns Hopkins Univ. Sch. Medicine, Baltimore, MD
J Supramol Struct; 4(4):467-473 1976

The mechanism of interferon action in human fibroblasts was studied by use of both antisera to human fibroblast interferon and the antisera to the surface of human fibroblast cell. The anti-interferon serum completely neutralized the antiviral effect of human fibroblast interferon. When added to the medium of the cells in which interferon synthesis had already been induced by poly (I;C), interferon antiserum prevented the intracellular antiviral state from developing. This prevention suggests that development of the antiviral state involves interferon interaction with the external part of the producing cell. Treatment with the serum directed against the surface of human fibroblast cells did not inhibit the antiviral activity of human interferon in these cells. The effect of gangliosides on the antiviral activity of human interferon was also studied. Human interferon bound to gangliosides; this interaction led to inactivation of the antiviral

effect of interferon. Pretreatment of human fibroblasts with gangliosides had no effect on the sensitivity of these cells to exogenous interferon. These results indicate that additional factors may be involved in the specificity of interferon recognition.

170. ROLE OF THE MEMBRANE-BOUND RECEPTOR SYSTEM IN THE BIOLOGICAL ACTIVITY OF INTERFERON.

Chany C, Pauloin A, Chany-Fournier F
Institut National de la Sante et de la Recherche Medicale U.-43, Hopital St Vincent de Paul, 74 avenue Denfert, Paris 75014, France
Tex Rep Biol Med; 35:330-335 1977

The model of the interferon receptor system initially proposed in 1973 is now supported by many independent observations and can be described with somewhat more precision. The cell membrane-bound receptor system consists of a nonspecific binding site made up of gangliosides (such as GM2). The activator site is probably formed by glycoproteins. It is likely that interferon has to interact with both sites at the surface of the cell membrane. The activator site carried probably the interferon species specific properties of the receptor, while all the other metabolic steps necessary for the development of antiviral activity are not species specific. The cooperation (resulting most likely in small aggregates) will change the conformational state of the membrane in a way compatible with the action of interferon. We postulate that many other cellular effects of interferon, such as priming, modification of antigenic properties, changes in membrane permeability, increase or decrease in sensitivity to toxins, and repression of cellular DNA synthesis could be secondary effects related to cell membrane modulation. Experiments are now in progress to prove or disprove these postulates. (Author abstract) (20 Refs)

171. SPECIFICITY OF BINDING OF INTERFERON TO CELLS.

Kohno S, Umino Y, Saito S
Dept. Measles Virus, Natl. Inst. Health of Japan, 3260 Nakato, Musashimurayama, Tokyo 190-12, Japan
Tex Rep Biol Med; 35:293-296 1977

A short review of the specificity of interferon binding to cells considers the question of whether interferon bound to the cell surface triggers the cellular responses leading to the establishment of antiviral potency, or whether there is a more critical cell-interferon interaction in the expression of its biological activities. There is no qualitative change in interferon which has reacted with cells. Cell binding and releasing of interferon occurs much more rapidly than the development of max resistance, so interaction between cells and interferon in initiating the cellular antiviral state may be a loose association or a reversible hit on the 'specific site' on the cell surface; max stimulation would then require continuation of hits. These sites apparently are located solely on the exterior surface of the cell membrane. There are probably at least two types of cell-interferon interactions: one is the binding not immediately related to the expression of interferon message, and another is an effective association (interaction with 'specific site') resulting in stimulation of the antiviral state. The species specificity of the antiviral action of interferon is not absolute. (18 Refs)

172. ENHANCEMENT OF INTERFERON ACTIVITY BY A MEMBRANE GLYCOPROTEIN RELATED TO THE TSH RECEPTOR (MEETING ABSTRACT).

Maheshwari R, Lazo P, Friedman R, Kohn L
Natl. Inst. Arthritis Metabolism and Digestive Disease, NIH, Bethesda, MD, 20205
J Clin Hematol Oncol; 9(4):282 1979

Thyrotropin (TSH) inhibition of interferon bioactivity in mouse Ly cells was associated with specific plasma membrane TSH binding sites. TSH binding was accounted for by membrane glycoproteins which can be solubilized with lithium diiodosalicylate (LIS) and reconstituted in liposomes. Purification of glycopeptides derived from TPCK tryptic digests of the LIS solubilized glycoprotein preparation yielded three fractions which interacted with TSH. Two of these enhanced interferon antiviral activity 10-to 100-fold in mouse Ly cells but not in human interferon sensitive or insensitive (KB) human cells. Enhanced antiviral activity was specific for mouse interferon, occurred after cells were preincubated with the glycopeptides, and was associated with specific binding of the glycopeptides to the cell. Analogous binding did not occur with similar fragments derived from human KB-3 cell glycoprotein preparations nor were these preparations bioactive. Substitution of a crude trypsin preparation for TPCK trypsin resulted in fragments which inhibited rather than enhanced antiviral activity. The characteristics of the bioactive fragments and their relationship to both TSH and interferon receptor function are under further investigation. (no Refs)

173. INTERFERON ACTION AND THE CELL SURFACE.

Friedman RM
Lab. Experimental Pathology, NIAMDD, NIH, Bethesda, MD, 20014
Pharmacol Ther [A]; 2(2):425-428 1978

Aspects of interferon action which may involve the cell surface are reviewed. Interferon appears to bind to the cell surface; this binding is necessary but not sufficient for the development of antiviral activity. Interferon binding appears to be required for the establishment of the antiviral state, and is followed by alterations in the plasma membrane. Antiviral activity is discussed with respect to chromosome requirements for interferon action, requirements for transcription and protein synthesis, a possible role for cyclic AMP in induction of interferon action, requirement for virus infection or double-stranded RNA, and some similarities between development of antiviral activity and the mechanism of action of glycopeptide hormones. Inhibition of virus growth in interferon-treated cells is discussed with respect to inhibition of virus uncoating, viral transcription, viral translation in interferon-treated cells and their extracts, and the inhibition of terminal events in the replication cycle of murine leukemia viruses. Non-antiviral activities of interferon possibly related to the cell surface include inhibition of cell growth, enhancement of phagocytosis, and interferon-induced enhancement of the specific cytotoxicity of sensitized lymphocytes. (84 Refs)

174. USE OF THYROTROPIN AND CHOLERA TOXIN TO PROBE THE MECHANISM BY WHICH INTERFERON INITIATES ITS ANTIVIRAL ACTIVITY.

Kohn LD, Friedman RM, Holmes JM, Lee G
Lab. Biochemical Pharmacology, NIH, Bethesda, MD 20014
Proc Natl Acad Sci USA; 73(10):3695-3699 1976

The effects of thyrotropin (TSH) and cholera toxin on mouse L-cells and on KB-3 human cells infected with encephalomyocarditis virus were studied. Thyrotropin (10

uM) inhibited the antiviral activity of interferon, but when added after interferon had no effect. Both cholera toxin and TSH could block the antiviral activity of interferon, but TSH activity is distinct from that of cholera toxin in two respects: the concentrations of the two agents required (1 nanoM for cholera toxin and 10 uM for TSH) are significantly different; and the TSH effect was reversible, whereas the cholera toxin effect was not. The rationale for evaluating the ability of the two agents to alter the in vivo action of interferon was that interferon, like TSH or cholera toxin, might initiate its biological effect on cell function by binding to ganglioside or ganglioside-like cell surface receptors. An interferon interaction with membrane receptors in vitro could be quantified indirectly by its effect on the binding of I-labelled TSH to plasma membranes. The binding of interferon to the membrane is a primary event not requiring host cell functions, and this event appears to result in a change in the membrane. Interferon, like cholera toxin and TSH, may therefore have two active sites: one for receptor interaction, the other for initiating the subsequent steps of transmembrane penetration and biological activity. This would account for the ability of human interferon to interact with mouse cells and mouse or human interferon to interact with cells biologically unresponsive to interferon. (23 refs)

175. INTERFERON AND GLYCOPROTEIN HORMONES.

Friedman RM, Grollman EF, Chang EH, Kohn LD, Lee G, Jay FT

Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD, 20014

Tex Rep Biol Med; 35:326-329 1977

The relationship between the structure and function of interferon (IF) and receptors for glycoprotein hormones has permitted the use of thyrotropin and cholera toxin as probes for the mechanism of IF action. The binding of IF and the resultant changes are discussed, as well as the enhancing effect of cyclic AMP on interferon response. (24 Refs)

176. ANTIBODY NEUTRALIZATION STUDIES OF THE ANTIVIRAL ACTIVITIES OF HUMAN LEUKOCYTE INTERFERON ON DIFFERENT CELLS.

Havell EA

Trudeau Inst., Inc., Saranac Lake, NY

Arch Virol; 65(3/4):229-236 1980

Human WBC interferon and fibroblast interferon were titrated by inhibition of a single cycle of virus replication on different cells which vary in sensitivities to the action of human interferons. The interferon dose response curves were found to be regularly sigmoidal, exhibit similar slopes, and reflect the relative sensitivities of each cell type to the antiviral activities of the human interferons. The degree and pattern of antibody neutralization for a constant quantity of WBC interferon was determined on the various cell types by virus yield assays. The antibody neutralization curves reveal the quantity of antibody required to neutralize the antiviral activity of the WBC interferon on each of the different cells. Because of the high degree of sensitivity of the assay system, the presence of very low levels of antigenically distinct interferons in the preparation can be detected. (Author abstract) (10 Refs)

177. ABNORMAL BEHAVIOR OF INTERFERON-INDUCED ENZYMATIC ACTIVITIES IN AN INTERFERON-RESISTANT CELL LINE.

Verhaegen M, Divizia M, Vandenbussche P, Kuwata T, Content J

Departement de Virologie, Institut Pasteur du Brabant, 28, rue du Remorqueur, B-1040, Brussels, Belgium

Proc Natl Acad Sci USA; 77(8):4479-4483 1980

Interferon induces two double-stranded RNA-dependent enzymatic activities: an oligoisoadenylate synthetase that converts ATP to ppp(A2'p)n5'A, and a protein phosphokinase. We have explored the level and inducibility of these two enzymes in a human cell line (HEC-1) totally insensitive to both the antiviral and the anticellular actions of interferon. The activities of both enzymes are high in untreated cells and only minor changes occur after treatment with interferon, even at high concentrations. Interferon-treated HEC-1 cells do not contain an inhibitor of the oligoisoadenylate synthetase activity. The products of this HEC-1 oligoisoadenylate synthetase consist mainly of dimers, trimers, and tetramers as found in other cell lines after interferon treatment. The synthetase level is unaffected by treating the cells with anti-interferon antiserum, indicating that the results cannot be explained by a spontaneous low production of interferon by these cells. Furthermore, virus multiplication is not inhibited, even after treatment with interferon. These observations suggest that either the two enzymatic activities do not suffice for the establishment of an antiviral state in vivo or that a regulatory control mechanism, lost in these cells and common for both enzymes, is required for the expression of the antiviral action of interferon. This might explain both the constitutivity of the two enzymes and the interferon resistance observed. (Author abstract) (37 Refs)

178. EFFECT OF INTERFERON ON LYMPHOCYTE TRANSFORMATION AND NUCLEAR ANTIGEN PRODUCTION BY EPSTEIN-BARR VIRUS.

Menezes J, Patel P, Dussault H, Joncas J, Leibold W

Ste-Justine Hosp., 3175 Ste-Catherine Road, Montreal, Canada

Nature (Lond); 260(5550):430-432 1976

Interferon treatment of the B95-8 strain of Epstein-Barr virus (EBV)-infected BJA-B cells did not inhibit lymphocyte transformation by EBV. No significant differences were found in terms of the time required for lymphocyte transformation regardless of interferon concentration. This effect is supported by the fact that the formation of EBV-induced nuclear antigen could not be completely inhibited, even after 1 wk at high interferon concentrations. This incomplete inhibition could, however, be the result of a minor population of *interferon-resistant cells.*

179. SENSITIVITY OF VARIOUS HUMAN LYMPHOBLASTOID CELLS TO THE ANTIVIRAL AND ANTICELLULAR ACTIVITY OF HUMAN LEUKOCYTE INTERFERON. BRIEF REPORT.

Hilfenhaus J, Damm H, Johannsen R

Behringwerke AG, D-3550 Marburg/Lahn, W. Germany

Arch Virol; 54(3):271-277 1977

Eight lymphoblastoid cell lines were incubated with human leukocyte interferon (HIF: 1,000 or 4,000 units/ml; prepared from Newcastle disease virus-infected cells). All lines except Molt-4 (acute lymphatic leukemia) carried the Epstein-Barr virus (EBV) genome. One cell line (B95-8) was of EBV-transformed marmoset leukocytes; the others were of human origin. The RPMI1788 (healthy donor) and SKL1 (leukemia), cell lines were not EBV producers. The Daudi (Burkitt lymphoma), P3HR1 (Burkitt lymphoma), Diehl I (EBV-transformed leukocytes), and Kaplan (infectious mononucleosis) cell lines were EBV producers. The Diehl I

and P3HR1 cell lines were sensitive to both the anticellular and antiviral activities of HIF. The B95-8, Kaplan, Molt-4, SKL-1 and RPMI1788 cell lines were insensitive to both actions of HIF. The Daudi cell line was highly sensitive to the anticellular action of HIF, but its sensitivity to the antiviral action of HIF could not be evaluated in the test system used (infection with Semliki Forest virus, which propagates poorly in Daudi cells). (22 Refs)

180. INDUCTION OF DELTA(4)3 KETOSTEROID SYNTHESIS BY INTERFERON IN MOUSE ADRENAL TUMOR CELL CULTURES.

Chany C, Mathieu D, Gregoire A
Institute de Recherches Scientifiques sur le Cancer, C.N.R.S., B.P. 8, Villejuif, France
J Gen Virol; 50(2):447-450 1980

Interferon, like cholera toxin, induces in mouse adrenal Y1 cells the production of delta(4)3 ketosteroids. In parallel, cyclic AMP (cAMP) is activated. At high concentrations, mouse but not human interferon induces a cell rounding effect, similar to that obtained with cholera toxin. In *Y1 cells transformed by simian adenovirus 7,* production of cAMP is still increased but that of steroids is blocked. The role of interferon in these cellular events is discussed. (Author abstract) (20 Refs)

181. DECREASED SENSITIVITY TO INTERFERON ASSOCIATED WITH IN VITRO TRANSFORMATION OF X-RAY-TRANSFORMED C3H/10T1/2 CELLS.

Brouty-Boye D, Gresser I, Baldwin C
Institut de Recherches Scientifiques sur le Cancer, 94800 Villejuif, France
Int J Cancer; 24(2):261-265 1979

We have compared the interferon sensitivity of parental 10T1/2 cells, having a phenotype characteristic of normal cells, with that of transformed cells isolated after x-irradiation or treatment with methylcholanthrene. Transformed cells were 10- to 20-fold less sensitive than the parental untransformed cells to the antiviral action of interferon and were also less sensitive to the inhibitory effect of interferon on cell multiplication. The decreased sensitivity of these cells to interferon is a useful marker of the transformed phenotype. (Author abstract) (15 Refs)

182. ANTIVIRAL AND ANTICELLULAR EFFECTS OF INTERFERON ON THE MOUSE EMBRYONIC CELLS TRANSFORMED BY VIRUSES AND/OR CHEMICAL CARCINOGEN.

Hajnicka V, Borecky L
Inst. Virology, Slovak Acad. Sciences, Bratislava, Czechoslovakia
Acta Biol Med Ger; 38(5/6):821-827 1979

The antiviral and/or anticellular actions of mouse interferon (IF) on C3H mouse embryo fibroblast (MEB) cell lines transformed by simian virus 40 (MEB-SV40), mouse sarcoma virus (MEB-MSV), or 2-methylcholanthrene (MEB-MCH) were studied. The transformed cells possessed different properties. All transformed cells were agglutinated by Concanavalin A, although their sensitivities to the lectin varied. Only MEB-SV40 cells were able to grow in soft agar. Only MEB-MSV cells produced IF; these were also the only cells able to cause tumor growth in nude mice following sc inoculation. MEB-MSV cells were 10-to 50-fold less sensitive than the other cell lines to the antiviral effect of IF. MEB-MCH and MEB-SV40 cells showed a 30% growth inhibition after treatment with 1,000 and 3,000 units of IF, respectively; because of the low sensitivity of MEB-MSV to the antiviral action of IF, a 30% inhibition of growth could not be registered. It was suggested that the varying sensitivities of transformed cells to the antiviral and anticellular activities of IF reflect the fact that different mechanisms are responsible for these activities. (22 Refs)

183. THE CELL-GROWTH INHIBITORY EFFECT OF INTERFERON. STUDIES OF A RESISTANT CELL-SUBLINE.

Borecky L, Fuchsberger N, Hajnicka-Gondova V, Ciampor F, Altaner C
Inst. Virology, 809 39 Bratislava, Czechoslovakia
Neoplasma; 24(2):125-137 1977

Factors that regulate the sensitivity of mouse L-cells to the cell-growth inhibitory effect (CGIE) of interferon (IF) were investigated. Although LB2 and CSV (an LB-2 subline obtained after prolonged passages in the presence of IF) did not differ in gross morphology, electron microscopy showed alterations both in cytoplasms and surface structures of the CSV cells. Viral particles were not found by electron microscopy in nonactivated CSV cells, but a significant amount of RNA-dependent DNA polymerase was found, suggesting that only the provirus was present while release of virus (C-type particles) was depressed. Resistance of CSV cells toward the CGIE of IF decreased after prolonged passages in the absence of IF, treatment of cells with 5-iododeoxyuridine, and treatment of cells with cyclic AMP (cAMP) and/or prostaglandin E2 (PGE2) (with theophylline). A similar effect was achieved in CSV cells and in primary mouse embryo fibroblasts after prolonged passages in vitro or infection of the cells with the mouse sarcoma virus-Harvey strain. Agglutinability of CSV cells with concanavalin A differed from that of LB2 cells. Since both cAMP and PGE2 (with theophylline) enhanced the CGIE sensitivity of CSV cells but had no effect on LB2 cells, it seems likely that the enhancing effect was mediated through the pathway PGE2-cAMP enhanced sensitivity. These data indicate that the viral background in the cell is more than incidentally associated with the CGIE of IF and that the activated endogenous and/or exogenous viral infection might be the factor that modifies the cell surface and thus the sensitivity of the cell to the CGIE of IF. (35 Refs)

184. STIMULATING EFFECT OF MOUSE SARCOMA VIRUS ON THE MULTIPLICATION OF NEWCASTLE DISEASE VIRUS.

Perries J, Canivet M, Olivie M, Boiron M
St. Louis Hosp., Paris, France
J Gen Virol; 14:207-208 1972

In Swiss mouse embryo cells (SMEC) preinfected with 1 focus-forming unit/cell of murine sarcoma virus-Moloney (MSV-M) and infected 48 hr later with 10 embryo infectious doses/cell of Newcastle disease virus (NDV), about 100 times more NDV was produced than in normal NDV-infected cultures, suggesting that the MSV-M blocks the action of the interferon produced by NDV. Interferon production in MSV-M infected cells treated with UV-inactivated NDV was the same as that in uninfected control cells. However, cells innoculated with MSV-M and treated with inactivated NDV were not protected against the cytopathic effect of vesicular stomatitis virus. This indicated that the mechanism of interferon production was unaffected by MSV-M despite inhibition of the antivirus effect of interferon, suggesting the possibility that MSV-M improved the infective yield of NDV by decreasing the cellular sensitivity to the antiviral action of interferon.

185. STUDIES ON INTERFERON AND MURINE LEUKEMIA SARCOMA VIRUS GROUP.
Peries JR, Canivet M, Boiron M
St. Louis Hosp., Paris, France
Bibl Haematol; (39):331-334 1973

Studies on the relationship between interferon and the murine leukemia and sarcoma virus complex are reviewed. Murine RNA tumor viruses do not induce detectable levels of interferon in vivo or in vitro, but these viruses are sensitive to the antiviral action of interferon. For instance, focus formation by Moloney sarcoma virus (M-MSV) and virus yield are significantly reduced in cells pretreated with interferon preparations. When JLSV5 cells chronically infected with Rauscher murine leukemia virus (R-MLV) are treated with interferon, modified virions are formed which do not contain the same amount of RNA as the prototype C-type particles. Mouse embryo cells chronically or acutely infected with R-MLV, Moloney murine leukemia virus, or M-MSV showed a decrease in sensitivity to interferon when the latter was titered on vesicular stomatitis virus as challenge virus. Data from several experiments suggest that the mechanism of decreased sensitivity to interferon depends on the effect of murine RNA oncogenic viruses at a level involving the final steps of the mechanism of interferon. Both Newcastle disease virus and Sendai virus multiply better in embryo cells preinfected with M-MSV.

186. EFFECT OF CELL DENSITY ON DEVELOPMENT OF THE ANTIVIRAL STATE IN INTERFERON-PRODUCING CELLS: A POSSIBLE MODEL OF IN VIVO CONDITIONS (39826).
Dianzani F, Viano I, Santiano M, Zucca M, Baron S
Dept. Microbiology, Univ. Turin, Turin, Italy
Proc Soc Exp Biol Med; 155(3):445-448 1977

Using tissue culture conditions which mimic the high cell densities in vivo, the interferon concentration was varied around producing cells by manipulating the extracellular volume. This was done to help define some of the variables which govern the action of interferon on the same cells which produce the interferon. Antiviral resistance was greater and developed more quickly in the concentrated cell suspensions. (11 Refs)

D.
Agents Which Inhibit or Potentiate Interferons' Antiviral Activity

187. POTENTIATION AND INHIBITION OF INTERFERON ACTION: ANTIVIRAL AND ANTITUMOR STUDIES.
Fleischmann WR
Dept. Microbiology, Univ. Texas Sch. Medicine, Galveston, TX, 77550
Med Pediatr Oncol; 9(1):89-92 1981

Observations are presented on two important aspects of the interferon (IF) system: potentiation and inhibition of the activities of IF. Potentiation is described with regard to initial observations, general nature, and possible mechanism of this phenomenon. It is noted that potentiation occurs when immune and virus-type IFs are mixed; in such mixtures, the antiviral and anticellular activities of IF are enhanced. In tumor model systems, combined IF preparations demonstrate a potentiation of both delay in tumor cell growth and in increased survival time caused by individual IFs. It was suggested that in vivo cancer therapy with combined IFs may be more effective than such therapy with a single type of IF. Inhibition of IF activity is described with regard to its pattern during production of immune IF, kinetics, and possible mode of action. It is noted that the inhibitor of IF action blocks both the antiviral and immunosuppressive activities of immune IF, but cannot reverse an established antiviral or immunosuppressive state. It is suggested that the inhibitor may play a natural role in the regulation of the activity of IF by decreasing the effectiveness of the IF present. (5 Refs)

188. LACK OF ASSOCIATION BETWEEN THE ELEVATION OF ADENOSINE 3',5'-CYCLIC MONOPHOSPHATE AND THE POTENTIATION OF THE INTERFERON-INDUCED ANTIVIRAL STATE BY NORADRENALINE IN NORMAL AND TUMORAL RAT CELLS.
Coupin G, Illinger D, Poindron P
Universite Louis Pasteur, UER des Sciences Pharmaceutiques, Laboratorie de Virologie et Microbiologie generale, 3, Rue de l'Argonne, F-67083 Strasbourg Cedex, France
Intervirology; 13(1):54-57 1980

Rat interferon (IF) induced a moderate and persistent elevation of cyclic AMP (cAMP) after 2 hr of contact with rat embryo fibroblasts (REFs), whereas in rat glial tumoral C6 cells IF did not enhance cAMP. Noradrenaline potentiated the antiviral state of REFs treated for 2 hr or more with IF and increased cAMP in these cells, but it did not potentiate the IF-induced antiviral state of C6 cells. However, as the control cells, IF-treated C6 cells responded to catecholamines by a 100-fold or more increase in cAMP. This suggested that cAMP was not primarily involved in the establishment of the antiviral state. (Author abstract) (13 Refs)

189. THE RELATIONSHIP BETWEEN ADENOSINE 3':5'-CYCLIC MONOPHOSPHATE (CAMP) AND INTERFERON ACTIVITY IN MOUSE CELLS.
Goldberg SJ, O'Shaughnessy MV, Stewart RB
Dept. Microbiology and Immunology, Queen's Univ., Kingston, Ontario K7L 3N6, Canada
J Gen Virol; 48(2):377-381 1980

Three mouse cell lines (L, 3T3, and SV3T3) were studied with respect to the elevation of cellular cAMP levels following interferon treatment, and the effect of stimulators of cAMP levels on the antiviral activity of interferon. Interferon treatment resulted in increased cAMP levels in L and 3T3 cells but not in SV3T3. The antiviral activity of interferon in cells treated with epinephrine and 1-methyl-3-isobutyl xanthine (stimulators of cAMP levels) was potentiated in L cells, but not in 3T3 cells and was lost in SV3T3 cells. (Author abstract) (18 Refs)

190. INCREASE OF INTERFERON ANTIVIRAL ACTIVITY BY EXOGENOUS CYCLIC ADENOSINE-3':5'-MONOPHOSPHATE (CAMP).
Koblet H, Wyler R, Kohler U
Inst. Medical Microbiology, Univ. Berne, Friedbuhlstrasse 51, CH-3008 Berne, Switzerland
Experientia; 35(5):575-576 1979

Some effects of cAMP on replication of Semliki Forest virus in chick embryo fibroblast cell cultures are described. Depending on concentration, the incorporation of [3H]-uridine into viral RNA or the formation of plaque-forming units is inhibited; the highest concentration tested was 8 milliM. Cyclic AMP has an effect of its own and increases the interferon action in the lower concentration ranges of interferon (up to 1 unit/ml). The effect of cyclic AMP is fast, needs no induction and is also visible in late phases of viral replication. However, these experiments do not estab-

lish a causal relation between cAMP and interferon. (Author abstract) (19 Refs)

191. ENHANCEMENT OF THE BIOLOGICAL EFFECTS OF INTERFERON BY ASSOCIATED TREATMENTS (MEETING ABSTRACT).

Chany C, Bourgeade MF, Cerutti I
Institut National de la Sante et de la Recherche Medicale U43, Hopital St.-Vincent-de-Paul, 74 avenue Denfert-Rochereau, 75014 Paris, France
J Clin Hematol Oncol; 9(4):276 1979

The interferon used for therapeutic trials is at present expensive to prepare. In addition, high concentrations of this substance can induce adverse effects. We have, therefore, studied the effect of substances which can enhance cellular immunity in vivo and thus balance the repressive effect of interferon on cell metabolism. We show, furthermore, that by manipulation of the cell membrane receptor, a similar increase in antiviral protection and anticellular effect can be obtained both in vitro and in vivo. (no Refs)

192. EFFECT OF DIBAZOL AND ASCORBIC ACID ON ANTIVIRUS ACTIVITY OF HUMAN INTERFERON IN CELL CULTURE.

Povolotskii IaL, Krivokhatskaia LD
Lab. Microbiology and Virology, A. I. Kolomiichenko Inst. Otorhinolaryngology, Kiev, USSR
Antibiotiki; 24(4):291-294 1979

The effects of Dibazol (DZ) and the ascorbic acid (AA) on the antivirus activity of human interferon (IF) were investigated. IF isolated from tonsil specimen stimulated by Newcastle disease virus was added to a primary human embryonal fibroblast (HEF) that was infected with vesicular stomatitis virus. Addition of DZ at 5 ug/ml caused greater than 3x increase in the IF activity. AA at 10 ug/ml caused 1.4x increase in the activity of IF with 1:16-1:32 titer, compared with 4.2x increase in the activity of IF with less than 1:8 titer. (20 Refs)

193. THE ACTIONS OF INTERFERON ARE POTENTIATED AT ELEVATED TEMPERATURE.

Heron I, Berg K
Basel Inst. Immunology, 487 Grenzacherstrasse, Postfach 4005, Basel 5, Switzerland
Nature (Lond); 274(5670):508-510 1978

Elevated incubator temperatures potentiate the antiviral activity, the killer-augmentory properties and the growth-inhibitory action of interferon on the lymphoblastoid cell line Daudi. The effect of temperature (37 C to 40 C) on antiviral activity of interferon was determined in human embryonic lung cultures challenged with vesicular stomatitis virus. The antiviral activity of interferon was increased more than threefold when the temperature was increased from 39 C to 40 C. The effect of interferon on lymphocyte killer activity was assayed using a one-way mixed lymphocyte reaction (MLR). At different times, mostly 6 days, after initiation of cultures, cell-mediated lympholysis (CML) activity was measured. Titration of interferon from 0-10,000 units/ml in MLR demonstrated that at 37 C and 39 C optimal enhancement of the CML product occurred at the same interferon concentrations (200-1,000 units/ml). In an experiment with six different allogeneic combinations with 500 units of interferon/ml, specific kills at 37 C and 39 C (especially at 39 C) were enhanced compared with cultures without interferon. When tested at 37 C, 38 C, 39 C and 40 C, the interferon growth inhibition of lymphoblastoid human B cell line Daudi increased markedly with increasing temperature. (15 Refs)

194. INACTIVATORS OF FIBROBLAST INTERFERON FOUND IN HUMAN SERUM.

Cesario T, Vaziri N, Slater L, Tilles J
Univ. California, Irvine, CA, 92664
Infect Immun; 24(3):851-855 1979

Investigation of the inactivators of fibroblast interferon has shown that these substances could be identified in every specimen of serum taken from normal individuals. These inactivators were found to destroy a mean of 82% of the interferon antiviral activity beyond that caused by the effects of temperature alone. The inactivators exerted no effect at 4 C but were found in a variety of animal as well as human sera. Although slight differences were found to exist in the extent of inactivation when comparing normal human serum to serum from patients (i) receiving chronic hemodialysis, (ii) with jaundice, or (iii) with underlying malignancies, the differences did not appear to be clinically significant. In exploring the nature of the substances, we found that both dialyzable and nondialyzable inactivators exist, but the former appear to be the major factors responsible for the unwanted process. (Author abstract) (9 Refs)

195. EFFECT OF SERUM ON THE ANTIVIRAL AND ANTICELLULAR ACTIVITIES OF MOUSE INTERFERON.

Kading VH, Blalock JE, Gifford GE
Dept. Immunology, Univ. Florida Coll. Medicine, Gainesville, FL
Arch Virol; 56(3):237-242 1978

Fetal bovine serum markedly decreased the ability of mouse L 929 interferon preparations to inhibit the formation of L-929 clones, but did not affect their ability to inhibit vesicular stomatitis virus (VSV) plaque formation in these cells. This dissociation of effects by interferon preparations indicates that: 1. the mechanism of action of interferon for its anticlonal and antiviral activities is different; or 2. the molecule responsible for the anticlonal activity is a separate growth inhibitory factor. (Author abstract) (25 Refs)

196. INACTIVATION OF HUMAN INTERFERON BY BODY FLUIDS.

Cesario TC, Tilles JG
Dept. Medicine, Div. Infectious Diseases, Univ. California, Irvine, CA, 92668
Tex Rep Biol Med; 35:443-448 1977

We have shown that almost all samples of serum, saliva, cerebrospinal fluid, fecal extract, bile or urine tested contain a substance or substances capable of inactivating human interferon at normal body temperature. This adverse effect appears to be greater for fibroblast interferon-induced by either polynucleotides or viruses, than for leukocyte interferon induced by viruses. These results have a number of implications for the clinical utilization of this natural antiviral substance. (Author abstract) (6 Refs)

197. IME - AN INHIBITOR OF INTERFERON ACTIVITY ISOLATED FROM MOUSE EMBRYONIC TISSUES. II BIOLOGICAL CHARACTERISTICS.

Cembrzynska-Nowak M
Virological Lab., Polish Acad. Sciences, Czerska 12, 53-114 Wroclaw, Poland
Arch Immunol Ther Exp (Warsz); 27(1/2):229-239 1979

The biological properties and mode of action of IME, an inhibitor of interferon activity isolated from mouse embryo, are discussed. IME was extracted from homogenized and lyophilized mouse embryos. Interferon inhibitory activity of IME was demonstrated, and anti-interferon activities of various tissues from pregnant mice and mouse embryos were compared. The levels of IME in mouse tissues were shown

to decrease with age, reaching the low level generally found in adult animals. IME had no effect on the replication of the indicator virus and did not function by direct inactivation of interferon nor by inhibition of its production. Inhibitor was added to cultures before and at various intervals after interferon to determine which stage of anti-viral activity of interferon is affected by IME. Anti-interferon activity of IME appeared only when IME was added to the cultures 4 hr after interferon. Additional experiments were designed to determine if pretreatment with interferon of cells exposed to IME was necessary for the appearance of anti-interferon activity. Scintillation counting was used to measure the incorporation of 14C-uracil in RNA nucleotides of cells treated with various concentrations of Actinomycin D (0.1 and 0.5 ug/ml) and IME (diluted 1:5) at 37 C for 2 hr. Actinomycin D almost totally abolished the anti-interferon action of IME, although it had no effect on replication of the indicator virus. In similar studies using cyclohexi.nide (1 ug/ml) instead of actinomycin D, IME activity appeared to be totally inhibited. IME was also seen to directly enhance the synthesis of RNA and proteins. (21 Refs)

198. PRODUCTION AND FUNCTION OF AN INHIBITOR OF INTERFERON ACTION FOUND IN MOUSE LYMPHOKINE PREPARATIONS (MEETING ABSTRACT).

Fleischmann WR, Lefkowitz EJ, Georgiades JA, Johnson HM
Univ. Texas Medical Branch, Galveston, TX, 77550
J Clin Hematol Oncol; 9(4):275 1979

Mouse lymphokine preparations contain an inhibitor which blocks interferon action. The inhibitor was first detected in mouse spleen cell supernatant fluids 72 hr after stimulation with the T-cell mitogen staphylococcal enterotoxin A. The inhibitor was also detectable in supernatant fluids of cells stimulated with concanavalin A and phytohemagglutinin P, though the kinetics of production of the inhibitor were different. Unstimulated cultures did not produce this factor. The inhibitor, purified 1,000-fold by two-step column chromatography, blocked the antiviral activity of up to at least 400 units of interferon. The inhibitor was resistant to digestion by trypsin, stable at pH 2, and stable at 60 C for 2 hr. When inhibitor was added as late as 3 hr after interferon, it blocked both the antiviral and immunoregulatory functions of interferon. Since the inhibitor blocked the function of both immune and fibroblast interferon, it may play a natural role in the regulation of the interferon system. (no Refs)

199. ISOLATION, PRELIMINARY CHARACTERIZATION, AND INTERFERON ANTAGONISTIC EFFECT OF A MAMMALIAN LECTIN-LIKE SUBSTANCE (MEETING ABSTRACT).

Chany-Fournier F, Paulonin A, Chany C
U43, I.N.S.E.R.M., Hopital St. Vincent de Paul, 74 av Denfert-Rochereau, 75014 Paris, France
Biol Cell; 36(3):3a 1979

We have isolated from mouse costal cartilage a tissue antagonist of interferon (TAI) which accelerates the decay of an established antiviral state. The effect is reminiscent of substances previously isolated from the basement membrane of human amnion. Since we have recently shown that phytohemagglutinin can mimic the biological effect of TAI, we have explored the possibility that TAI could be an animal lectin-like material. First, TAI agglutinates mouse cells; second, this cell agglutination is inhibited by some sugars. Preliminary characterization indicates the active molecule is a protein. After Sephadex G-100 gel filtration, TAI is found in a peak of 150,000 mol wt. When purified by isoelectric focusing, this peak shows max activities corresponding to an isoelectric point of pH 8.8. TAI binds to polysaccharide residues to the cell membrane which could be its primary site of action, comparable to phytohemagglutinin. (no Refs)

200. A TISSUE ANTAGONIST OF INTERFERON DERIVED FROM MOUSE CARTILAGE WITH PROPERTIES SIMILAR TO THAT OF VEGETABLE LECTINS.

Chany-Fournier F, Paulcin A, Chany C
Unite de Recherche sur les Infecions Virales U 43, Hopital Saint-Vincent-de-Paul, 74, av Denfert-Rochereau, 75014 Paris, France
C R Acad Sci [D] (Paris); 185(8):941-944 1977

It has recently been observed that phytohemagglutinin (PHA) suppresses the antiviral state in cells in a manner similar to that of tissue antagonists of interferon (TAI). The cell-agglutinating properties of TAI prepared from thorax cartilage of Swiss mice against murine fibroblasts and L-929 cells were compared with those of PHA in this study. Various concentrations of TAI or PHA were added to cultures of cells which were incubated for 2 hr at 37 C. The agglutination rate was defined as the greatest dilution at which 50% of the cells were agglutinated. For TAI, the agglutination rate in the L-929 preparations was 128 and for the same cells, the rate for PHA was 10,000. Of 10 hexoses tested for their ability to inhibit the cell-agglutinating activity of TAI and PHA for L-929 cells, only D-glucosamine, 2-deoxy D-glucose and D-galactosamine were found to be active (0.25 ml of 0.1 M solution of hexose and 0.25 ml of 1 g solution of TAI). The TAI from the mouse cartilage was also tested for its ability to restore the sensitivity of L-929 cells previously incubated with interferon to infection with encephalomyocarditis virus. (12 Refs)

201. FACTORS ANTAGONISTIC TO THE ANTIVIRAL ACTIVITY OF INTERFERON, EXTRACTED FROM VARIOUS HUMAN SARCOMAS.

Chany C, Lemaitre J, Gregoire A
Inst. Cancer Res., Villejuif, France
C R Acad Sci [D] (Paris); 269(25):2628-2630 1969

Evidence of in vitro tumor-stimulating or anti-interferon activity was investigated in extracts from 18 human angio-, myxo-, chondro-, fibro-, reticulo- or rhabdomyosarcomas, as compared to both untreated controls and controls which were pretreated with extracts of normal muscle tissue derived from each of the same donors. When embryonal BALB/c mouse cells were incubated with the extracts, prior to washing and infecting with mouse hepatitis virus, pretreatment with the tumor extracts resulted in an increase of 2-10 times the infectious virus titer on L cells in 15/15 instances, as compared to untreated controls. Cells which were pretreated with extracts of normal muscle tissue were entirely negative in 24/30 instances, positive in only 6/30. In a correlative study, L cells were treated with various conc of interferon, then with tumor or muscle-tissue extracts, prior to being infected with Indiana strain vesicular stomatitis virus. The sarcoma extracts inhibited the antiviral activity of interferon significantly; the muscle-tissue extracts showed somewhat less than 50% the same inhibitory activity. Both heating to 56 C for 1 hour and the addition of trypsin partially inactivated the inhibitory activity of the sarcoma extracts; and had no effect on the activity of the muscle-tissue extracts.

202. FACTORS ANTAGONISTIC TO INTERFERON, EXTRACTED FROM TUMORS INDUCED BY MOUSE SARCOMA VIRUS IN THE HAMSTER.

Chany C, Gregoire A, Lemaitre J
CNRS Cancer Res. Inst., Villejuif, France
C R Acad Sci [D] (Paris); 269(13):1236-1237 1969

Tumor cells of a strain (T-MSV) obtained by inoc newborn hamsters with Moloney mouse sarcoma virus were inoc im into 3-week-old hamsters. Extracts derived from the resulting tumors were incubated with cells derived from Balb/c mouse embryos, prior to washing the preparations and incubating them with mouse hepatitis virus (MHV) for 3 multiplication cycles. As compared to controls, the multiplication of MHV was increased by 3-10 times, in 11/18 experiments. In a collateral study, L cells were treated with 20-40 or 200-400 U interferon, and then (after the interferon was removed) incubated with preparations of tumor extracts of hamster as above, prior to washing and infecting them with Indiana strain vesicular stomatitis virus. The extracts inhibited the antiviral effects of interferon significantly, at both interferon dose levels. Their activity was equal to 10-100 times the inhibitory activity of control extracts of muscle tissue cells, derived from the contralateral side of the tumor-bearing animals. The activity of the tumor extracts was not destroyed by trypsin or by heating to 56 C for 1 hour, nor was its production limited to any particular cell type.

203. EFFECTS OF CONCANAVALIN A ON THE ANTIVIRAL AND CELL GROWTH INHIBITORY ACTION OF HUMAN INTERFERONS (MEETING ABSTRACT).

Kuwata T, Fuse A, Takayama N, Morinaga N
Sch. Medicine, Chiba and Komagome Hosp., Chiba Univ., Tokyo, Japan
Abstracts of a Conference on Regulatory Functions of Interferons, held in New York, October 23-26, 1979. New York Academy of Sciences, New York, NY, pp. 18, 1979.

Human transformed cells, reticulosarcoma A (RSa), were sensitive to cytotoxicity of concanavalin A (Con A) and about 10% of control cells survived after treatment with 25 ug/ml of Con A for 6 days. The interferon-resistant subline, IFr, was less sensitive to Con A than RSa. When RSa cells were treated with 200 units/ml of WBC interferon and at the same time with 20 ug/ml of Con A, the agents acted synergistically and marked enhancement of the suppression of cell growth was observed. The same results were obtained with fibroblast interferon and also by using other cell lines. Con-A resistant sublines, Con Ar-1 and Con Ar-3, were isolated from RSa cells. Con Ar cells were sensitive to antiviral and cell growth inhibitory actions of interferon. At the concentration of 50 ug/ml, Con A did not affect antiviral action of interferon in RSa or in Con Ar cells. (no Refs)

204. DEGRADATION BY PHYTOHEMAGGLUTININ OF THE ANTIVIRAL STATE INDUCED BY INTERFERON.

Pauloin A, Chany-Fournier F, Epstein L, Chany CH
Institut national de la Sante et de la Recherche Medicale, Unite 43, hopital Saint-Vincent-Rochereau, 75014 Paris, France
C R Acad Sci [D] (Paris); 284(12):1119-1122 1977

The degradation of the murine interferon induced antiviral state of L929 cells by phytohemagglutinin (PHA) was investigated. Both the M and P forms of the mitogen degraded the antiviral state and restored virus sensitivity to the cells. The degradation was dependent on the amount of the lectin, the contact period with the cell and the presence of PHA membrane receptors. The importance of the membrane configuration not only in the induction but also in the maintenance of the antiviral state is discussed. (10 Refs)

205. CHOLERA TOXIN AND ITS B SUBUNIT INHIBIT INTERFERON EFFECTS ON VIRUS PRODUCTION AND ERYTHROID DIFFERENTIATION OF FRIEND LEUKEMIA CELLS.

Belardelli F, Ausiello C, Tomasi M, Rossi GB
Servizio Biologica, Instituto Superiore di Sanita, Viale Regina Elena 299, 00161 Rome, Italy
Virology; 107(1):109-120 1980

Treatment of Friend leukemia cells with cholera toxin or with its purified B subunit inhibits the interferon (IFN)-induced reduction of Friend virus release and of virus yields after exogenous infection with vesicular stomatitis virus. Likewise, the 'enhancement' of erythroid differentiation of DMSO-treated Friend cells induced by low doses of crude or semipurified IFN is completely abolished. These results, confirmed with pure IFN preparations, are in keeping with the hypothesis that an early interaction with the cell membrane is a necessary step for the establishment of these different IFN effects. In addition, they indicate that the increased cyclic AMP levels, induced by the whole toxin, do not play a significant role in these phenomena; rather they may be due to the lectin-like activity of the B subunit. Evaluation of reciprocal dose-response curves of IFN and cholera toxin shows that treatment with toxin concentrations as low as 10(-13) M induces a major inhibition of IFN effects. A millionfold higher toxin concentration does not substantially increase the toxin actions. The toxin-induced redistribution of membrane gangliosides is discussed as a possible mechanism of the observed inhibition of IFN activities. (Author abstract) (29 Refs)

206. ESTABLISHMENT OF THE INTERFERON-MEDIATED ANTIVIRAL STATE: ROLE OF FATTY ACID CYCLOOXYGENASE.

Pottathil R, Chandrabose KA, Cuatrecasas P, Lang DJ
Dept. Pediatrics, Duke Univ. Medical Center, Durham, NC, 27710
Proc Natl Acad Sci USA; 77(9):5437-5440 1980

Inhibitors of fatty acid cyclooxygenase (8,11,14-icosatrienoate, hydrogen donor:oxygen oxidoreductase, EC 1.14.99.1) were found to suppress the establishment of the interferon-mediated antiviral state. The prevention, by these compounds, of the development of interferon protection correlated with the degree as well as the duration of cyclooxygenase inhibition. Anti-inflammatory substances lacking cyclooxygenase inhibitory activity did not interfere with the establishment of interferon protection. The addition of exogenous prostaglandins was not found to replace the need for a functional cyclooxygenase and, in some instances, could be shown to diminish the establishment of interferon protection. It is proposed that fatty acid cyclooxygenase is an essential component in the optimal induction of the interferon antiviral state. (Author abstract) (22 Refs)

207. PROSTAGLANDIN A COMPOUNDS AS ANTIVIRAL AGENTS.

Santoro MG, Benedetto A, Carruba G, Garaci E, Jaffe BM
Center Virology, Consiglio Nazionale delle Ricerche, O.O.R.R. Via Circonvallazione Gianacolense 85, Rome, Italy
Science; 209(4460):1032-1034 1980

Prostaglandins of the A series strongly inhibit the production of Sendai virus in African green monkey kidney cells and are able to prevent the establishment of persistent infection ('carrier' state). This action is specific for prostaglandin A and is not due to alteration in the host cell metabolism or

in the virus infectivity. The possibility that this effect is mediated by *interferon* is discussed. (Author abstract) (18 Refs)

208. POSTTRANSCRIPTIONAL EFFECT OF DEXAMETHASONE AND INTERFERON ON THE VIRAL REPLICATION INDUCED BY IODODEOXYURIDINE FROM MURINE TRANSFORMED NONPRODUCER FIBROBLASTS.

Wu AM, Schultz A, Reitz MS, Gallo RC
Bionetics Res. Lab., 7300 Pearl St., Bethesda, MD 20014
Bibl Haematol; (43):475-480 1976

The authors give data indicating that dexamethasone and interferon work antagonistically both at a translational step to affect synthesis of virus proteins and at a posttranslational step to affect the assembly or release of virus particles. The production of murine type C virus was induced from K-BALB cells by 24-hr iododeoxyuridine (IUdR) treatment. Dexamethasone (10**-6 M) and/or interferon (200 U/ml) were then added. Both affected the production of v2 xenotropic virus from K-BALB cells but not the v1 N-tropic virus. Thus, two viruses with different tropisms in the same host are subjected to different regulatory mechanisms. A posttranscriptional effect of dexamethasone was indicated by (1) a maximal stimulation observed 24-48 hr after IUdR treatment; (2) the fact that cordycepin does not suppress virus production when added after dexamethasone, but does when it is added before; and (3) the fact that dexamethasone stimulated only the cells already producing virus. Measurement of the concentration of group-specific proteins by complement fixation indicated a tenfold increase of virus production in the presence of dexamethasone, but no change in the amount of intracellular virus components. Interferon inhibited the synthesis of viral components at the early period after induction but not the late period. If cells were treated with both drugs, the interferon-induced inhibition was partially overcome, but the concentration of intracellular virus components was higher than in cells not treated with interferon. (24 refs)

209. SYNTHESIS OF TYPE C VIRUS PARTICLES FROM MURINE-CULTURED CELLS INDUCED BY IODODEOXYURIDINE.

Wu AM, Schultz A, Gallo RC
Dept. Molecular Biology, Bionetics Res. Lab., Bethesda, MD 20014
J Virol; 19(1):108-117 1976

Dexamethasone (dex) and interferon were used to study the mechanisms involved in the synthesis of type C viruses in murine K-BALB cells following induction of virus production by iododeoxyuridine (IUdR). Interferon inhibited the production of xenotropic C virus induced by IUdR from K-BALB cells both in the absence and presence of dex, but it did not affect the production of N-tropic C virus. Exposure of the cells to interferon for longer than 12 hr was required for maximum effect. Two types of inhibitory effects were observed: one diminished by dex when the steroid was added 24 hr after interferon removal and the second resistant to dex. The concentration of intracellular group-specific antigen was diminished after interferon and increased after dex exposure. When induced cells were treated with both interferon and dex, the intracellular group-specific protein concentration was slightly increased, but virus production was reduced tenfold compared with induced cells treated with dex alone. It is concluded that *interferon* and dex may affect both the synthesis of viral proteins and the assembly or release of virus particles and that dex can partially nullify the inhibitory activity of interferon. The results also support previous conclusions that the regulatory mechanisms for the synthesis of viral proteins and for the release of viral particles may differ and that controls for xenotropic and ecotropic virus formation may not be identical. (25 refs)

210. ANTI-INTERFERON EFFECT OF REMANTADINE IN CULTURES OF HUMAN LYMPHOBLASTOID CELLS.

Novokhatskii AS, Kniazeva VF, Iushina SN, Cherkashina NP, Kadyrova AA
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Vopr Virusol; (4):481-483 1980

The anti-interferon effect of the anti-influenza drug Remantidine (RT) was studied in human B cells (Raji), forest Semliki virus system. Additive inhibition of virus reproduction was recorded at relatively high doses of interferon and RT, while at intermediate concentrations RT provided the anti-interferon effect. (9 Refs)

211. DIMINISHED ANTIVIRAL EFFECT OF HUMAN INTERFERON IN THE PRESENCE OF THERAPEUTIC CONCENTRATIONS OF ANTINEOPLASTIC AGENTS.

Cesario TC, Slater LM
Dept. Medicine, Univ. California, Irvine, CA, 92717
Infect Immun; 27(3):842-845 1980

Antiviral activity of human interferon has been found to be diminished in the presence of therapeutic concentrations of certain drugs used to treat neoplastic diseases. (Author abstract) (11 Refs)

212. ROLE OF RECEPTORS AND CYTOSKELETON IN REVERSE TRANSFORMATION AND STEROIDOGENESIS INDUCED BY INTERFERON (MEETING ABSTRACT).

Chany C, Rousset S, Bourgeade MF, Mathieu D, Gregoire A
INSERM U-43, Hop. St. Vincent de Paul, Paris, France
Abstracts of a Conference on Regulatory Functions of Interferons, held in New York, October 23-26, 1979. New York Academy of Sciences, New York, NY, pp. 20, 1979.

Cytoskeleton disrupting drugs block the establishment of the antiviral effect of interferon (IF) or induce its decay. Repair of defective cytoskeletal constituents by sodium butyrate in sarcoma cells results in an increased IF sensitivity. In murine sarcoma virus-transformed mouse cells carried for either short or long periods in the presence of IF, microfilament bundles appear and the number of desmosomes increases. We show that these cellular events play an important role in the induction of reverse transformation, bringing about a change in the phenotypic expression of such transformed cells, since they recover contact inhibition and lack colony formation in agar. The antitumor activity of IF in vivo could be at least in part related to this biological effect detected in vitro. In addition, in a suitable cell system, besides its antiviral effect, IF can induce the synthesis of ketosteroids. (no Refs)

213. EFFECT OF CYCLOHEXIMIDE AND PUROMYCIN ON THE ANTIVIRAL AND ANTICELLULAR ACTIVITIES OF HUMAN INTERFERON.

Kuwata T, Fuse A, Morinaga N
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
J Gen Virol; 37(1):195-198 1977

Human WBC interferon has antiviral activity and anticellular effects on the transformed human cell lines, RSa and RSb. Treatment of the cells with cycloheximide or puromycin at 0.5 to 5.0 microg/ml suppressed the antiviral action of interferon but increased its anticellular effects. Interferon also has antiviral activity in IFr cells, but this is relatively resistant to its anticellular action. Nevertheless, both drugs

suppressed the antiviral activity of interferon and increased its anticellular action. (Author abstract) (18 Refs)

214. THE EFFECT OF SODIUM BUTYRATE ON THE SENSITIVITY OF NORMAL OR MURINE SARCOMA VIRUS-TRANSFORMED CELLS TO INTERFERON.

Bourgeade MF
Unite 43 de INSERM, Hopital Saint-Vincent-de-Paul, 74, avenue Denfert-Rochereau, 75014 Paris, France
C R Acad Sci [D] (Paris); 287(4):391-394 1978

A study on the effect of sodium butyrate (SB) treatment on interferon sensitivity of embryonic cells from Balb/C mice transformed by Moloney murine sarcoma virus is reported. The effect of SB on interferon sensitivity of normal untransformed embryonic Balb/C mouse cells (FES) was also studied. When EMC cells were incubated with SB for 48 hr, trypsinated, and recultured with SB for 18 hr followed by treatment with interferon, viral growth was inhibited. Growth curves for EMC treated with interferon and SB simultaneously or interferon alone were almost identical indicating a failure of SB to affect sensitivity to interferon unless the cells were pretreated. Growth curves of FES cells pretreated with SB and then with interferon did not differ markedly from that of FES cells exposed to interferon alone indicating a failure of SB to affect interferon sensitivity of normal cells. It is hypothesized that the decreased response to interferon of transformed cells can be due, at least in part, to the disorganization of the microtubules and microfilaments. (8 Refs)

III. PRECLINICAL STUDIES OF INTERFERONS' ANTIVIRAL EFFICACY

A.
Immunologic Effects of Interferons Related to Antiviral Efficacy

215. SUMMARY: NATURAL IMMUNITY AND RESISTANCE AGAINST MICROBIAL AGENTS.

Herberman RB
Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD, 20205
Natural Cell-Mediated Immunity Against Tumors. Herberman RB, ed. New York, Academic Press, 1321 pp., 1980.

Experiments that suggest a possible role of natural killer cells (NK) in the in vivo control of viruses or of virus-infected cells are reviewed. Hamster tumor cells that have been persistently infected with various RNA viruses (eg, mumps, measles, and influenza) have not grown as well in nude mice. The ability of viruses to stimulate *interferon* (IF) production is important to the resistance to tumor growth. A similar role of NK cells and IF in some persistent human virus infections has also been observed. But results of one study have demonstrated no increased NK activity against target cells infected by a choriomeningitis (LCM) virus. Detailed experiments on the natural, genetically-determined resistance of some mice to lethal infection by influenza and other orthomyxoviruses have shown that genetic factors may affect natural resistance by influencing levels of NK activity, the degree of IF production in response to viruses or other stimuli, and the responsiveness of host cells to IF. (2 Refs)

216. INTERFERON AND NK CELLS IN RESISTANCE TO PERSISTENTLY VIRUS-INFECTED CELLS AND TUMORS.

Bloom B, Minato N, Neighbour A, Reid L, Marcus D
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY
Natural Cell-Mediated Immunity Against Tumors. Herberman RB, ed. New York, Academic Press, 1321 pp., 1980.

The resistance of athymic nude mice to tumor cells persistently infected (PI) with a variety of RNA viruses was examined. Since in vitro growth rates of uninfected and virus tumor cells could not be distinguished, it appeared that the failure of virus PI HeLa or BHK cells to form tumors in nude mice was a consequence of host response to the infected cells rather than to an intrinsic property of the cells. In vitro, virus PI HeLa cells were subject to spontaneous cytotoxicity by normal nude mouse spleen cells, whereas uninfected cells were not. Also in vitro, the virus PI tumor cells stimulated interferon (IF) production in normal nude mouse spleen cells, whereas the uninfected cells did not. The effector cells in this system did not appear to be conventional T cells, B cells, or macrophages, but shared some surface markers with human and animal T lymphocytes. Virus PI cell challenge of the nude mice resulted in increased natural killer (NK) activity. When the ability of unlabeled target cells to compete with labeled target cells was examined in cold competition experiments, the results showed that the effector cells were not totally nonspecific. It was also found that BK-mumps cells grew in the nude mice only after treatment with antibodies to mouse IF; this indicated that IF, possibly acting through NK cells, is involved in the resistance of athymic nude mice to the growth of virus PI tumor cells lines. Results of cell fractionation experiments supported the idea that NK effector cells and IF-sensitive cells are different subpopulations or are at different stages of differentiation. A strong parallel was suggested between susceptibility to NK cell killing in vitro and failure of PI tumor cells to produce tumors in vivo. In some patients with diseases such as multiple sclerosis, decreased IF production was noted. These results suggested that the NK-IF system is one of the critical factors in host defense against persistent viral infections and tumorigenesis. (21 Refs)

217. ANTIVIRAL EFFECT OF INTERFERON IN VIVO MAY BE MEDIATED BY THE HOST.

Schellekens H, Weimar W, Cantell K, Stitz L
Dept. Virology, Erasmus Univ., PO Box 1738, Rotterdam, The Netherlands
Nature (Lond); 278(5706):742 1979

Results indicating that protection by human WBC interferon against viral infection in vivo can occur without inhibition of viral replication of the same virus in vitro are reported. It is suggested that interferon may activate several defense systems of the host which can selectively destroy virus-infected cells in vivo. (7 Refs)

218. PILOT STUDIES WITH HUMAN INTERFERON IN HERPESVIRUS SAIMIRI-INDUCED LYMPHOMA IN OWL MONKEYS.

Rabin H, Adamson RH, Neubauer RH, Cicmanec JL, Wallen WC
Dept. Virology, Litton Bionetics, Inc., Kensington, MD 20795
Cancer Res; 36(2):715-719 1976

The nature of Herpesvirus saimiri (HVS)-induced disease in owl monkeys is described, and preliminary studies of its treatment with human interferon are reported. All monkeys inoc with HVS became chronically infected as determined by persisting antibodies. Approx. 80% developed lymphomatous disease, and of these, 80% developed peripheral

blood leukemia. The av survival time was 122 d, ranging from 56-203 d. Morphologic, cytogenetic, lymphoid subclass, and functional activity characteristics of the cultured tumor cells were described. The three most useful parameters for monitoring the course of the disease were: loss of responsiveness of peripheral lymphocytes to phytohemagglutinin (PHA) and concanavalin A; the appearance of peripheral blood lymphocytes that behaved as infectious centers for HVS when cocultivated with permissive cells; and the appearance and rise in titer of antibody to HVS-associated early antigen. Five lymphomatous monkeys were treated with human interferon after establishment of their disease. Interpretation of the results was difficult in three animals, since they were in an advanced stage of disease at the time of treatment; however, there was some reduction in WBC in these animals. The other two monkeys achieved temporary remissions. In one animal, 3 i.v courses of interferon given daily during 10-14 d periods (200,000-400,000 U/d) over a period of 66 d maintained the WBC in the normal range. The second animal was treated with 400,000 U/d x 14 d, during which time the WBC returned to normal. Coincident with the fall in WBC there was a return of response to PHA and pokeweed mitogen and a reduction in the number of infectious centers in the peripheral blood. It is suggested that interferon might have a role as an adjunct to immunotherapy. (37 refs)

219. MECHANISM OF RECOVERY FROM SYSTEMIC HERPES SIMPLEX VIRUS INFECTION. I. COMPARATIVE EFFECTIVENESS OF ANTIBODY AND RECONSTITUTION OF IMMUNE SPLEEN CELLS ON IMMUNOSUPPRESSED MICE.

Worthington M, Conliffe MA, Baron S
Dept. Medicine, St. Elizabeth's Hosp., 736 Cambridge St., Brighton, MA, 02135
J Infect Dis; 142(2):163-174 1980

The role of cellular immunity, humoral antibody, and *interferon* in recovery from primary systemic infection in mice due to herpes simplex virus Type 1 (HSV-1) was studied. Immunosuppression by three methods, each of which was sufficient to suppress humoral and cellular immunity, markedly potentiated primary systemic HSV-1 infection. Immunosuppressed mice did not form neutralizing antibody to HSV-1, but passive transfer of physiologic amounts of neutralizing antibody as late as day 6 after infection exerted a protective effect. Passive transfer of 10(8) immune spleen cells on day 3 after infection was only partially protective and did not thereafter reverse the effect of x-irradiation of HSV-1 infection. Furthermore, mice that received immune cells appeared to make sufficient antibody to explain the protective effect of the transferred cells. These results suggest that antibody to HSV-1 has a critical role in promoting recovery from primary infection in this model. The findings neither favor nor exclude a defensive role for immune cells in this experimental primary HSV-1 infection. (Author abstract) (39 Refs)

220. STUDIES OF THE CELLULAR IMMUNE RESPONSE OF MICE TO HERPES SIMPLEX VIRUS (HSV) (MEETING ABSTRACT).

Zawatzky R, Hirt HM, Becker H, Kirchiner H
Institut fur Virusforschung, Deutschen Krebsforschungszentrum, Heidelberg, W. Germany
Z Immunitaetsforsch; 155(1):76 1978

Mice injected ip with HSV die after 7-12 days from encephalitis. In our model we have compared C57BL/6 (B6) mice which are relatively resistant and DBA/2 (D2) mice which are quite susceptible to HSV infection. The LD50 between these two strains differed by a factor of several hundred. Previous studies have suggested that this difference was caused by differences in the cellular immune response of inbred strains, but definitive proof for this conclusion has been incomplete. We have now developed a sensitive assay to measure cellular immunity of mice to HSV by the in vitro production of the lymphokine *immune interferon* (IIF). Spleen cells from D2 mice in vitro produced only low levels of IIF after HSV infection at all times tested. In contrast, high levels of IIF were found in spleen cell cultures of B6 mice between 3 and 60 days after infection. Similar data were obtained when resistant B6D2F1 hybrids and susceptible BALB/c mice were compared. Also, after in vivo challenge with HSV, IIF was found only in the serum of B6 mice but not of D2 mice. Our data demonstrate the usefulness of the IIF assay in studies of the antiviral immune response and suggest the possibility that IIF may have an important in vivo role. (no Refs)

221. INTERFERON EFFECTS ON IMMUNOLOGICALLY ACTIVATED MURINE LEUKEMIA VIRUSES.

Hirsch MS, Black PH; Proffitt MR
Modulation of Host Immune Resistance in the Prevention or Treatment of Induced Neoplasias. Fogarty International Center Proceedings No. 28. NIH and John E. Fogarty International Center for Advanced Study in the Health Sciences, Bethesda, MD, 1977.

The effects of interferon (IF) were studied in two murine model systems in which a relationship had been established between immune disorders and activation of oncogenic C-type viruses. IF (O.1 ml) was injected ip bid into (BALB/c X A/J)F1 mice starting 1 day prior to the first ip injection of BALB/c spleen cells and continuing for 28 days; four weekly injections of BALB/c spleen cells were given. Spleens from mice sacrificed after 28 days were examined and assayed for mouse-tropic C-type viruses, and long-term survivors were examined for evidence of lymphoma. IF significantly reduced virus positivity in mice undergoing GVHR (graft-vs-host reaction) and completely prevented lymphoma development in these mice, compared with a 50% incidence in untreated GVHR mice. Examination of spleen showed that IF also reduced the severity of the GVHR itself. However, IF did not alter virus appearance following skin grafting and antilymphocyte serum (ALS) treatment. When IF (O.1 ml tid) was given ip, beginning 1 day prior to grafting and continuing until graft rejection was complete, to BALB/c mice receiving A/J grafts, the grafts had a median survival of 14 days in controls and 16 days in IF-treated animals. When BALB/c mice received DBA/2 grafts, the median survival of grafts was 16.5 days for controls and 20.5 days in treated mice. When BALB/c mice were grafted with A/J skin and treated with ALS (O.25 ml) twice weekly for 1 mo, with IF (O.1 ml) given tid starting 1 day prior to transplantation and continuing until 1 day prior to death, the immunosuppressive effects of IF enhanced ALS-mediated immunosuppression. 4/12 mice given IF and ALS maintained their grafts for 1 mo vs 2/12 controls, and among mice maintaining grafts, 5/6 were virus-positive compared with 6/18 of mice rejecting their grafts. Differences in IF effects in the two in vivo systems could not be explained on the basis of different IF sensitivities of the activated viruses. However, these superficially contrasting results may be explained by considering the antiviral and immunosuppressive effects of IF. (22 Refs)

222. THE INFLUENCE OF INTERFERON ON THE EXPRESSION OF TARGET CELL ANTIGENS RECOGNIZED BY CTL ON HERPES SIMPLEX VIRUS (HSV) INFECTED CELLS (MEETING ABSTRACT).

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Z Immunitaetsforsch Allerg Klin Immunol; 153(4):325-326 1977

Infection of mice with herpes simplex virus (HSV) results in the sensitization of antigen reactive T lymphocytes which, upon transfer into in vitro culture conditions, differentiate into the cytotoxic T lymphocytes (CTL). On the other hand, virus infection of cells results in the production of interferon which in turn blocks the replication of virus material in newly infected cells. Since virus specific CTL do recognize virus dependent cell surface antigens, we tested whether target cells infected in the presence of interferon would express cytotoxic determinants recognized by HSV specific CTL. The results clearly indicate that interferon can block the expression of target cell antigens on HSV-infected cells. One may conclude, therefore, that the protective effect of CTL during a virus infection is based on their capacity to destroy virus infected cells and that of interferon to block the virus infection of cells.

223. FURTHER STUDIES ON THE INHIBITION OF LYMPHOCYTIC CHORIOMENINGITIS-INDUCED GLOMERULONEPHRITIS BY ANTIINTERFERON GLOBULIN. CIRCULATING IMMUNE COMPLEXES AND ULTRASTRUCTURAL STUDIES.

Ronco P, Woodrow D, Riviere Y, Moss J, Verroust P, Guillon JC, Gresser I, Sloper JC, Morel-Maroger L
INSERM, U64, Hopital Tenon, 75970 Paris Cedex 20, France

Lab Invest; 43(1):37-46 1980

We have shown previously that the development of glomerulonephritis that follows neonatal infection of mice with lymphocytic choriomeningitis (LCM) virus was markedly inhibited by treatment of the mice with antimouse interferon antibody. To understand further this phenomenon, we have performed two different types of investigations. First, circulating immune complexes were measured in neonatally LCM virus-infected mice, treated with sheep antiinterferon antibody, normal sheep serum, or left untreated. Using three tests (virus-IgG complexes, Raji cell assay, and C1q binding assay) immune complexes were found in all three groups of mice infected with LCM virus. The levels were not significantly different in antiinterferon-treated mice, although the prevalence and severity of the glomerulonephritis were considerably decreased in this group until 80 days of age. Second, a sequential ultrastructural study of the early stages of the glomerulonephritis was performed in Swiss mice infected at birth with LCM virus and either left untreated or given injections of sheep antiinterferon antibody or normal sheep serum. By electron microscopy, abnormalities of the glomerular basement membrane, similar to those induced by exogenous interferon, could be detected in untreated mice infected at birth with LCM virus. The lesions characterized by thickening of the lamina rara interna containing areas of rarefaction, were transient: max at day 16, they were barely detectable by day 58. At this time, electron-dense deposits could be detected in the mesangial spaces. At day 185 and 216, these deposits had increased in size but could also be found in control noninfected mice. The injection of antiinterferon antibody could completely inhibit the development of the glomerular basement membrane lesions. We conclude from these observations that the protection provided by antiinterferon in the development of LCM virus-induced glomerulonephritis is not linked to a decreased amount of circulating immune complexes but may be due to the inhibition of the local action of interferon on the glomerulus. (Author abstract) (29 Refs)

224. IMMUNOREGULATORY ACTION OF TYPE I INTERFERON IN THE MOUSE (MEETING ABSTRACT).

De Maeyer E, De Maeyer-Guignard J
Institut Curie, Universite Paris-Sud, Orsay, France

Abstracts of a Conference on Regulatory Functions of Interferons, held in New York, October 23-26, 1979. New York Academy of Sciences, New York, NY, pp. 1, 1979.

The effect of type I interferon production on immunity to the interferon inducing virus was examined using the Newcastle disease virus (NDV)-mouse model and comparing If-1(h) and If-1(l) animals. The levels of neutralizing antibodies to NDV was not influenced by high or low interferon production. The degree of cell-mediated immunity, as measured by delayed hypersensitivity (DH) to NDV, was influenced by the levels of interferon produced. Anti-interferon globulin given right after immunization decreased sensitization to NDV, whereas additional, exogenous interferon, given to low interferon producers, stimulated sensitization to NDV. The alleles at the If-(1) locus influenced the extent of DH to NDV, in that the If-1(h) mice developed much stronger DH than did If-1(l) mice. However, results from recombinant inbred strains, F2 and backcross generations showed that for high interferon production to stimulate DH to NDV, other genes, present in the C57BL/6 background but as yet not characterized, are required. Thus DH to NDV is determined on the one hand by the alleles at If-1, influencing interferon production, and on the other hand by a combination of several genes affecting the interaction of interferon with cells of the immune system. (no Refs)

225. INTERFERON MEDIATES ENHANCEMENT OF TUMOUR GROWTH AND VIRUS-INDUCED SARCOMAS IN MICE.

Gazdar AF, Sims H, Spahn GJ, Baron S
Natl. Cancer Inst., Bethesda, Md.

Nature [New Biol]; 245(142):77-78 1973

Although interferon and its inducers have been reported to inhibit the growth of tumors in vivo or tumorigenic and diploid embryonic cells in vitro, interferon inducers have also been reported to accelerate the growth of transplanted and virus-induced tumors and to enhance spontaneous and virus-induced transformation in vitro, particularly when there is pretreatment with the inducers. In the present work, weanling BALB/c mice and suckling Osborne-Mendel rats were used. The interferon used was prepared from Newcastle disease virus-infected Moloney sarcoma virus transformed S+L- cells. Pretreatment of mice with a single dose of interferon or poly (I) poly (C) 6-24 hr before infection with MSV enhanced tumor size and incidence. Simultaneous administration of virus and interferon or poly (I) poly (C) gave more variable and less significant results, while administration of interferon or poly (I) poly (C) 24 hr after virus had no significant effect. The tumor enhancing effect of both substances was strongly dose-dependent. Pretreatment of rats with interferon had no effect on tumor induction while poly (I) poly (C) pretreatment had a moderate effect. It was suggested that the paradoxical effects of interferon and its inducers on tumor growth may be associated with their effects on the immune system. Thus, under certain circumstances, interferon and poly(I) and poly (C) act as immunological adjuvants, while pretreatment may depress immunological responsiveness.

226. THE TRANSFORMATION OF ADULT BUT NOT NEWBORN HUMAN LYMPHOCYTES BY EPSTEIN BARR VIRUS AND PHYTOHEMAGGLUTININ IS INHIBITED BY INTERFERON: THE EARLY SUPPRESSION BY T CELLS WITH EPSTEIN BARR INFECTION IS MEDIATED BY INTERFERON.

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Sidney Farber Cancer Inst., Harvard Univ., 44 Binney St., Boston, MA, 02115
J Immunol; 126(3):829-833 1981

In a previous study, it was demonstrated that T cells from adult individuals were able to suppress the transformation of B cells after infection by EBV. In this paper, it is shown that this suppression is mediated by interferon. Thus, the suppression is abrogated by anti-interferon serum and mimicked by human WBC interferon. Furthermore, the interferon is released in response to the virus-infected B cell, not the virus alone. The relevance of these results to previous clinical evidence, indicating a role for interferon in recovery from EBV infection is discussed. Interferon will also suppress the transformation of adult B lymphocytes by the mitogen phytohemagglutinin (PHA). However, interferon at concentrations 2 to 3 orders of magnitude higher was unable to suppress the transformation of neonatal B lymphocytes by either EBV or PHA. These experiments suggest that EBV and PHA induced transformation share a common interferon sensitive step. Lastly, the resistance of newborn lymphocytes to the protective effect of interferon may be an important consideration in the application of interferon as an antiviral or anti-tumor agent. (Author abstract) (27 Refs)

227. EPSTEIN-BARR HERPESVIRUS INFECTION: INHIBITION BY IMMUNOLOGICALLY INDUCED MEDIATORS WITH INTERFERON-LIKE PROPERTIES.

Lai PK, Alpers MP, MacKay-Scollay EM
Clinical Studies Unit, Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20014
Int J Cancer; 20(1):21-29 1977

When sensitized WBC from Epstein-Barr virus (EBV)-seropositive adults were reexposed to EBV antigen or to tuberculin-purified protein derivatives, they produced lymphokines. These lymphokines included migration inhibition factor, which inhibits the migration of guinea-pig peritoneal exudate cells, and other lymphokines with the characteristics of interferon, which inhibit EBV-induced transformation and EBV superinfection of target cells. Unsensitized WBC from seronegative adults and from neonates did not produce lymphokines when challenged with the antigens. This indicates that cell-mediated immunity and its associated soluble mediators may be involved in the control of EBV infection and that the interferon release assay is a useful in vitro correlate for the study of cellular immunity to EBV. (31 Refs)

228. MODE OF REGULATION OF NATURAL KILLER CELL ACTIVITY BY INTERFERON.

Minato N, Reid L, Cantor H, Lengyel P, Bloom BR
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
J Exp Med; 152(1):124-137 1980

The influence of interferon (IF) on natural killer (NK)-mediated cytolysis of virus-infected tumor cells was studied. In order to examine the ability of various tumor cell lines to stimulate IF production, normal spleen cells from BALB/c and CBA/N nude mice were cocultured with uninfected HeLa cells or virus persistently infected (PI) HeLa cells; PI HeLa cells stimulated IF production, while uninfected HeLa cells and supernatants from virus PI cell cultures did not. Immunological studies revealed that the phenotype of lymphocytes responsible for NK activity and IF production was Ly 5+, Qa+, ganglio-N-tetraosylceramide+, and that a subset of NK cells carries the Thy 1+ surface marker. Further studies suggested that the Ly 5 gene product was critically involved in the recognition and/or cytolytic process of NK cells. The possibility that supernatants containing IF might augment NK activity in vitro was examined by incubating spleen cells with supernatants of mixed lymphocyte-tumor cell cultures; such incubation for 3 hr resulted in a substantial increase in subsequent lysis of virus PI HeLa cells. The use of chemically-homogeneous purified mouse IF confirmed that this augmentation was due to IF itself and not to some contaminant. Examination of the kinetics of lysis of virus-infected cells in the presence and absence of anti-IF antibodies indicated that lysis observed early in this NK assay was independent of IF production in the assay culture and represented a reliable assay of preexisting NK activity. Studies of the mode of augmentation of NK activity by IF suggested that IF induces Ly 5-, Qa 5+ precursors to express both NK activity and the associated Ly 5 surface component. (27 Refs)

229. NATURAL KILLER CELL ACTIVITY AGAINST VIRUS-INFECTED CELLS.

Santoli D, Perussia B, Trinchieri G
Wistar Inst. Anatomy, Biology, Philadelphia, PA
Natural Cell-Mediated Immunity Against Tumors. Herberman RB, ed. New York, Academic Press, 1321 pp., 1980.

The effect of virus infection of fibroblasts (F) or other human target cells on lymphocyte natural cytotoxicity was measured by 51Cr release. Peripheral blood lymphocytes from randomly selected healthy donors were significantly more cytotoxic in vitro against allogeneic virus-infected F (measles, subacute sclerosing panencephalitis, paramyxovirus-1, mumps, herpes simplex type-1, influenza, or rabies) than against uninfected F. Human fetal skin F or other human target cells that had been infected several hr before addition to lymphocytes were lysed more efficiently than uninfected target cells. The rate at which virus-infected and uninfected F were killed remained the same for 3 hr after addition of the lymphocytes; however, increased incubation times resulted in sharply increased cytotoxicity in virus-infected targets. Increased cytotoxicity against infected cells was observed in lymphocyte preparations from all donors tested; however, the relative cytotoxicity levels varied with different donors and in different experiments. Natural killer cells were responsible for the observed cytotoxicity. *Interferon* induced on exposure of lymphocytes to virus-infected F appeared to be responsible for the enhanced cytotoxicity of the NK cells. (5 Refs)

230. SPONTANEOUS CYTOTOXICITY AGAINST VIRUS-INFECTED CELLS: CELLULAR IMMUNOADSORPTION ON INFECTED CELL MONOLAYERS.

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Dept. Pharmacology, Duke Univ. Medical Center, Durham, NC, 27710
J Immunol; 125(3):1387-1394 1980

Peripheral blood lymphocytes of normal adult donors were demonstrated to be cytotoxic in a short-term 51Cr-release assay to a cell line persistently infected with Sendai virus, SV-HEp2, to a far greater extent than to uninfected HEp2 cells. The cytotoxicity was not inhibited by Fab fragments of anti-human Fab fragments, nor did its occurrence depend upon the presence of fetal calf serum, indicating that antibodies were not required for cytotoxicity. Lymphocytes

were separated into adherent and nonadherent fractions by cellular immunoadsorption on SV-HEp2 monolayers. Both fractions were depleted of cytotoxic activity when assayed immediately after the separation, whereas immunoadsorption on uninfected HEp2 monolayers failed to deplete cytotoxic activity. When SV-HEp2-adherent and nonadherent lymphocytes were incubated overnight before assay, the cytotoxic activity of the nonadherent fraction remained low, whereas that of the adherent fraction was increased as much as four-fold above control levels. Substantial titers of interferon-like antiviral activity were detected in 18-hr-culture supernatants of SV-HEp2 adherent, but not nonadherent, lymphocytes. The addition of exogenous *interferon* to the nonadherent fraction failed to augment its cytotoxic activity, however. We concluded that cellular immunoadsorption on SV-HEp2 monolayers removed a population of lymphocytes with cytotoxic potential and that interferon induced in the adherent lymphocyte fraction augmented the cytotoxicity of this fraction after overnight incubation. (Author abstract) (45 Refs)

231. SPONTANEOUS CYTOTOXICITY MEDIATED BY HUMAN MONOCYTE-MACROPHAGES AGAINST HUMAN FIBROBLASTS INFECTED WITH HERPES SIMPLEX VIRUS-AUGMENTATION BY INTERFERON.

Stanwick TL, Campbell DE, Nahmias AJ
Dept. Pediatrics, Emory Univ. Sch. Medicine, 69 Butler St., SE, Atlanta, GA, 30303
Cell Immunol; 53(2):413-416 1980

Human monocyte-macrophages (Mphi) displayed spontaneous cytotoxicity for human fibroblasts infected with herpes simplex virus (HSV). The HSV-immune status of the Mphi did not affect the spontaneous cytotoxicity. Significant cytotoxicity required an effector cell to target cell ratio of at least 50:1, and was first observed 12 hr after incubation of Mphi with HSV-infected cells. A 12-to 18-hr preincubation of Mphi with interferon enhanced the cytotoxic activity. Cytotoxicity activity was also observed with cytomegalovirus-infected HF implying that the cytotoxic activity of the Mphi was nonspecific for viral-infected cells. (Author abstract) (21 Refs)

232. INTERFERON-SENSITIVE EXPRESSION OF MEMBRANE-BOUND IGM ON A HUMAN LYMPHOID B CELL LINE PERSISTENTLY INFECTED WITH HERPES SIMPLEX VIRUS.

Menezes J, Bourkas AE
Lab. Immunovirology, Dept. Microbiology and Immunology, Univ. Montreal, Montreal H3T 1C5, Canada
Biomedicine [Express]; 31(1):2-4 1979

The expression of Fc receptors and other surface immunologic markers by a B cell type lymphoid cell line persistently infected with herpes simplex virus (HSV) was compared with that of uninfected Raji cells and their primarily HSV-infected counterparts. Approx 50% of primarily and persistently HSV-infected cells expressed Fc receptors. However, unlike the primarily HSV-infected cells, about 80% of the persistently-infected cells were positive for surface IgM. No other classes of immunoglobulin were detected. IgM induction could be suppressed by long-term treatment with human leukocyte interferon but not with phosphonoacetic acid (an inhibitor of herpesvirus DNA polymerase activity). Removal of interferon did not restore IgM expression within 90 days. When Raji-A44 cells were superinfected 15 days after the removal of interferon, about 40% expressed Fc receptors. (7 Refs)

233. EFFECT OF VIRUS INFECTIONS ON TARGET CELL SUSCEPTIBILITY TO NATURAL KILLER CELL-MEDIATED LYSIS.

Welsh RM, Hallenbeck LA
Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
J Immunol; 124(5):2491-2497 1980

By using two types of target cells (L-929, Vero) infected with several different viruses (Herpes simplex (HSV), lymphocytic choriomeningitis, Sendai, Sindbis, and vesicular stomatitis) that code for proteins expressed on the cell surface,the interactions of natural killer (NK) cells with virus-infected target cells were examined. When cells were exposed to normal endogenous spleen WBC from C3H/St mice, slightly elevated levels of natural killing were usually observed against virus-infected but not uninfected targets. Exposure of virus-infected cells to spleen WBC preparations taken from lymphocytic choriomeningitis virus (LCMV)-infected mice and thus containing activated NK cells resulted in a strikingly different effect. If short-term (4 hr) assays were run to avoid additional NK cell activation by interferon, virus-infected targets were frequently less sensitive to natural killing than control cells. This apparent paradox is explained by the fact that virus infections that activate NK cells may also protect targets. HSV-infected Vero cells resisted NK cell lysis, failed to bind lymphocytes in target binding assays, and were poor competitors in cold target binding assays, indicating that they no longer expressed a functional NK target antigen. Sendai virus-infected L-929 cells resisted NK cell lysis but bound lymphocytes to an enhanced degree and acted as excellent cold target competitors. *Interferon* treatment rendered L-929 cells resistant to natural killing and unable to inhibit in competition assays. These results indicate that the interactions between NK cells and virus-infected targets are complex and vary with the virus, target cell, and extent of infection. (Author abstract) (20 Refs)

234. SUPPRESSION OF IN VITRO GROWTH OF VIRULENT AND AVIRULENT HERPES SIMPLEX VIRUSES BY CELL-MEDIATED IMMUNE MECHANISMS, ANTIBODY, AND INTERFERON.

Shimizu F, Satoh J, Tada M, Kumagai K
Natl. Inst. Dental Res., Bethesda, MD, 20014
Infect Immun; 22(3):752-757 1978

A rounding cell-forming -GC strain, which is a variant of a syncytial giant cell-forming herpes simplex virus (+GC Miyama strain), was highly attenuated for Swiss, BALB/c nu/nu, and nu/+ mice, whereas +GC was highly virulent to all the mice tested. +GC and -GC were antigenically indistinguishable from each other by cross-neutralization and cross-immunization. Immunosuppression induced by cyclophosphamide converted the nonlethal -GC infection of mice into a fatal infection. -GC replication in tissue culture was more effectively suppressed by spleen cells immunized with either +GC or -GC than was the +GC replication. -GC replication was also inhibited more effectively by antibody or the antibody-dependent cell-mediated system than was the +GC replication. -GC is highly sensitive to mouse interferon, but +GC was relatively resistant. These findings indicate that attenuation of this avirulent -GC strain may be due to a high susceptibility of its replication to humoral and cell-mediated defense factors. The probable roles of each defense factor in recovery from the infection with virulent and attenuated herpes simplex virus are also discussed. (Author abstract) (27 Refs)

235. INTERFERON ENHANCES T-CELL MEDIATED CYTOTOXICITY OF H-2 COMPATIBLE TARGET CELLS INFECTED WITH UV-INACTIVATED HERPES SIMPLEX VIRUS. BRIEF REPORT.

Sethi KK, Brandis H
Institut Medizinische Mikrobiologie Immunologie, Universitat Bonn, Bonn-Venusberg, W. Germany
Arch Virol; 57(2):177-183 1978

Mouse L-cells infected with UV-inactivated herpes simplex virus (HSV) could serve as suitable targets for monitoring H-2 restricted cytotoxicity mediated by HSV-immune T cells. Cytotoxic potential of immune T cells for H-2 compatible targets exposed to UV-inactivated HSV was enhanced if the latter were pretreated with mouse interferon. (Author abstract) (19 Refs)

236. DIFFERENTIATION OF THE IMMUNOSUPPRESSIVE AND ANTIVIRAL EFFECTS OF INTERFERON.

Johnson HM
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Cell Immunol; 36(2):220-230 1978

Virus-induced (virus-type) interferon suppression of the in vitro antibody response of mouse (C57Bl/6) spleen cells to sheep RBC was blocked by 5 x 10**-5 M 2-mercaptoethanol (2-ME). The blockade was not due to a direct effect on interferon since 2-ME was capable of blocking the suppression when added to cultures up to 48 hr after interferon. 2-ME blockade of virus-type interferon immunosuppression was not due to the immunoenhancing property of 2-ME. Similar protective effects of 2-ME were observed during immunosuppression by virus-type interferon inducers, but not T-cell mitogen inducers of interferon (immune interferon). The data suggest that the immunosuppressive properties of virus-type and immune interferon preparations involve different mechanisms. Virus-type interferon inhibited DNA synthesis in unstimulated spleen cell cultures and in 2-ME stimulated cultures, and the degree of inhibition of DNA synthesis appeared to be related to the immunosuppressive property of interferon in the absence or presence of 2-ME. 2-ME did not affect the antiviral properties of either virus-type or immune interferon in nonlymphoid cells. Further, the induction of virus-type interferon in spleen cells was neither inhibited nor enhanced by 2-ME, while the induction of immune interferon was enhanced. This enhancement is consistent with 2-ME enhancement of the immunosuppressive effects of immune interferon inducers. There are two possibilities for 2-ME blockade of the immunosuppressive effect of virus-type interferon, while not affecting the antiviral property. Firstly, the immunosuppressive and antiviral properties of virus-type interferon may involve different mechanisms at the subcellular level. Secondly, the selectivity of the blockade by 2-ME could be due to the fact that spleen cells are the target cells in immunosuppression, while L cells are the target cells in inhibition of virus replication. Thus, virus-type interferon may suppress the immune response at the level of the macrophage and 2-ME may reverse this effect by replacing a blocked macrophage function. (Author abstract) (36 Refs)

B.

Antiviral Efficacy of Interferons In Vivo

237. HUMAN LEUKOCYTE INTERFERON PRODUCED BY E. COLI IS BIOLOGICALLY ACTIVE.

Goeddel DV, Yelverton E, Ullrich A, Heyneker HL, Miozzari G, Holmes W, Seeburg PH, Dull T, May L, Stebbing N, Crea R, Maeda S, McCandliss R, Sloma A, Tabor JM, Gross M, Familletti PC, Pestka S
Dept. Molecular Biology, Genentech Incorporated, 460 Pt. San Bruno Blvd., San Francisco, CA, 94080
Nature (Lond); 287(5781):411-416 1980

A human leukocyte interferon (LeIF) cDNA was enzymatically synthesized, inserted into the vector pBR322, and cloned in Escherichia coli. The DNA sequence codes for a 23-amino acid signal peptide followed by an interferon polypeptide of 165 amino acids. An expression plasmid was constructed which permits the synthesis in E coli of 2.5 x 10(8) units of interferon per liter of culture. This LeIF protected squirrel monkeys from lethal encephalomyocarditis virus infection. (Author abstract) (39 Refs)

238. EFFECTIVE ANTIVIRAL PROPHYLAXIS AND THERAPY BY SYSTEMIC APPLICATION OF HUMAN INTERFERON IN IMMUNOSUPPRESSED MONKEYS.

Neumann-Haefelin D, Shrestha B, Manthey KF
Dept. Virology, Univ. Freiburg, Postfach 820, D-78 Freiburg, W. Germany
J Infect Dis; 133(Suppl):A211-A216 1976

Antiviral therapy and prophylaxis by systemic application of human interferon (INF) in immunosuppressed monkeys are described. Rhesus monkeys treated with antilymphocytic globulin were infected with Medical Lake macaque Herpesvirus or vaccinia virus. Monkeys not treated with INF developed pustulous reactions at the sites of inoculation of vaccinia virus. Injected im (either for 7 days starting on the 1st day of primary reaction or from 1 day before to 3 days following infection), 500,000 IU/day human WBC INF decreased the development of the secondary lesions only. A vesicular rash similar to that of human varicella was caused by infection with Herpesvirus. The disease was averted in 2/4 monkeys; the rash was delayed in the other two, through prophylactic treatment with INF. In all monkeys, if therapy was begun when the lesions appeared, their growth was prevented. The results suggest systemic treatment with INF might be effective for immunosuppressed patients. (19 refs)

239. INFLUENCE OF INTERFERON ON THE REPLICATION OF ONCOGENIC HERPESVIRUSES IN TISSUE CULTURES AND IN NONHUMAN PRIMATES.

Laufs R, Stienke H, Jacobs C, Hilfenhous J, Karges H
Hyg. Inst., U. Gottingen, W. Germany
Med Microbiol Immunol (Berl); 160(4):285-294 1974

The sensitivity of H saimiri (HVS) and H ateles (HVA) to human interferon (HIF) was determined using owl monkey kidney (OMK) cell cultures. Both of these oncogenic herpesviruses were relatively insensitive to the action of interferon. The virus multiplication could be inhibited when the cells were pretreated with high concentrations of interferon (4000 British Standard (BRS) U/ml). The degree of protection against HVS was improved when the cells were kept in interferon medium after challenge with the virus. The replication of HVS during cocultivation of lymphoid carrier cells with permissive indicator cells was studied. The transition of the HVS genome in the lymphoid cells from the latent to the productive stage could not be inhibited by interferon. High doses of HIF did not prevent the development of malignant lymphoma induced by HVS or HVA in CT marmoset monkeys. The survival time after infection with HVS was prolonged in one of the HIF-treated mon-

keys (334 BRS U/g followed by 66 U/g every 2nd day postinfection), while tumor development induced by HVA was not influenced by HIF (400 BRS U/g followed by 80 U/g every 2nd day postinfection).

240. BOVID HERPESVIRUS 2: EPIZOOTIOLOGY, PERSISTENCE, AND EFFECTS OF TEMPERATURE ON PATHOGENESIS.

Letchworth GJ
Cornell Univ., Ithaca, NY, 14850
Diss Abstr Int [B]; 41(1):76 1980

Bovid herpesvirus 2 (BHV-2) is the cause of bovine herpes mammillitis, an acute vesicular disease of the teat and udder skin of dairy cattle, and primarily affects heifers at calving. Although only small amounts of virus are found in internal tissues of diseased animals, large quantities are demonstrated in the skin. Satisfactory explanation for this distribution has not been offered nor has the mode of transmission of BHV-2 been demonstrated. Proof for the persistence of virus in recovered animals was sought by explant culturing of tissues from eight seropositive cattle. Cultures were maintained for 49-72 days, but BHV-2 was not isolated. Apparent transmission of BHV-2 was detected by the seroconversion of most of 32 bulls during a subclinical epizootic in 1/8 barns. The remainder seroconverted later while stabled adjacent to recovered bulls. Explantation of the limitation of viral growth to the skin was provided by experiments in which skin temperature of cows was artificially altered to 1-3 C above the rectal temperature on one side, and 2-9 C below rectal temperature on the other side. BHV-2 lesions in the 'cold' skin had up to 1010x as much infectious virus as lesions in 'hot' skin. Peak *interferon* titers in lesion biopsies, but not serum antibody or cellular infiltration of lesions, were associated with cessation of viral growth. The inhibitory effect of heat on BHV-2 lesions was attributed principally to direct suppression of viral growth. The immune response was probably more vigorous in 'hot' skin. In vitro interferon production was temperature-dependent. Bovine interferon effectively protected cells against BHV-2 at 39-40 C, but not 30 C. Effects of antibody on virus or virus infected cells, the effect of peripheral WBC on infected cells, and the bovine delayed hypersensitivity skin reaction, however, were not significantly temperature dependent. Nevertheless, an inverse relationship between the effects of temperature on BHV-2 replication and the principal immune response (interferon) in BHV-2 lesions was demonstrated in vitro. At high temperature (40 C), BHV-2 replication was suppressed, and interferon was produced in amounts that fully protected cells against the virus. At low temperature (30 C), however, BHV-2 replicated to high titers, but interferon production was greatly diminished and large amounts were not effective in protecting cells against BHV-2. Therefore, virus would be expected to grow in skin exposed to low environmental temperatures, but not in the relatively warmer internal organs. This same inverse relationship may also explain the appearance of severe lesions in heifers at calving. Such animals normally have severe postparturient udder edema that interferes with the circulation of warm blood to the skin. (no Refs)

241. ROLE OF INTERFERON IN THE PATHOGENESIS OF HERPES SIMPLEX VIRUS DISEASE IN MICE.

Gresser I, Tovey MG, Maury C, Bandu MT
Institut de Recherches Scientifiques sur le Cancer, Villejuif, France
IARC Sci Publ; 24(II):1049-1054 1978

The role of interferon in the pathogenesis of herpes simplex virus (HSV) disease was studied in pathogen-free Swiss and C3H mice. Iv administration of a sheep antimouse interferon globulin resulted in the early appearance of disease and death, and it increased the overall mortality due to HSV type 1 injected ip or sc. The enhancing effect was most striking when HSV was inoculated sc. Twenty-five mice that had survived HSV inoculation were injected iv with antiinterferon globulin 18 days after virus inoculation. In no instance did this treatment induce signs of HSV disease. These results demonstrate the importance of the early interferon response in the pathogenesis of HSV disease in mice. (7 Refs)

242. EFFECT OF INTERFERON ON SYSTEMIC HERPESVIRUS INFECTIONS.

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Dept. Pediatrics, Univ. Utah Coll. Medicine, Salt Lake City, UT, 84132
Tex Rep Biol Med; 35:472-477 1977

The studies reviewed here are encouraging in that herpes simplex virus (HSV) is moderately sensitive to the action of interferon and that infections in experimental animals clearly may be altered by exogenous interferon and interferon inducers. On the other hand it is apparent that the potential of this approach to treatment of herpesvirus infections is limited by the levels of interferon that can be passively administered or induced, the development of hyporeactivity which prevents maintaining high levels of interferon in infected animals after inoculation of inducers, and the failure to alter the course of HSV infection once the virus is established in target organs. (Author abstract) (17 Refs)

243. EFFECT OF EXOGENOUS INTERFERON ON NEONATAL INFECTION WITH MURINE CYTOMEGALOVIRUS.

Cruz JM, Waner JL, Dammin GJ
Dept. Immunology, Inst. Medical Microbiology, Univ. Gothenburg, Gothenburg, Sweden
IARC Sci Publ; 24(II):1067-1071 1978

The prophylatic value of exogenous interferon (IF) was tested in vivo in mice. IF was produced in mouse embryo cells (ME) inoculated with murine cytomegalovirus (MCMV). Within 24 hr of birth, mice were given 0.1 ml ip of the undiluted interferon preparation or 0.1 ml of mock IF, and 24 hr later, 50% of the animals in each group received either 100 plaque forming units of MCMV ip or virus diluent. On day 12, the animals were sacrificed, and the blastogenic response of spleen lymphocytes to phytohemagglutinin (PHA) or lipopolysaccharide (LPS) was determined. The background incorporation of 3H-thymidine was higher in lymphocyte cultures from animals treated with IF than in those from animals that received mock IF. When IF was given before MCMV, the extensive hepatocellular necrosis and cellular infiltration noted in control mice were not present. IF alone caused no tissue damage. Fewer MCMV were found in the submaxillary glands of animals treated with IF than in those given mock IF. (5 Refs)

244. ROLE OF INTERFERON IN THE PATHOGENESIS OF VIRUS DISEASES IN MICE AS DEMONSTRATED BY THE USE OF ANTI-INTERFERON SERUM. VI. POLYOMA VIRUS INFECTION.

Gresser I, Maury C, Kress C, Blangy D, Maunoury MT
Institut de Recherches Scientifiques sur le Cancer, Villejuif, France
Int J Cancer; 24(2):178-183 1979

The effect of a single ip injection of potent sheep antimouse interferon globulin (SAIG, 50-100 ul) on polyomavirus (PV)-induced early runting disease and tumor formation was studied using Swiss mice. Mice treated with PV (50 ul ip immediately before SIG during the first 24 hr of

life) grew as well as mice treated with PV + SAIG for the first 11 days, after which 10%-20% of the PV-treated mice and most of the PV + SAIG-treated mice were runted. Mortality during the first 2 mo was 0%-25% for the PV-treated mice and 70%-100% for the PV + SAIG-treated mice. Deaths usually occurred during the third or fourth week. Histologic examination showed no differences between mice treated with PV and those treated with PV + SAIG. The median tumor-inducing doses for the PV- and PV + SAIG-treated mice were 10(5) and 10(2)-10(3) plaque-forming units, respectively. The tumor incidence was greater and the tumor latent period reduced in mice treated with PV + SAIG compared with those given PV alone. The sites of tumor development were similar in the two groups. The titers of virus in the thymuses and spleens of the PV + SAIG-treated mice were greater than those in the PV-treated mice. No interferon was demonstrated in the PV-treated mice, whether or not they were given SAIG. The results suggest that interferon is an important factor in determining the susceptibility of newborn mice to PV. (33 Refs)

245. INTERFERON IN EXPERIMENTAL VIRAL INFECTIONS IN MICE: TISSUE INTERFERON LEVELS RESULTING FROM THE VIRUS INFECTION AND FROM EXOGENOUS INTERFERON THERAPY.

Heremans H, Billiau A, De Somer P
Rega Inst., Univ. Leuven, Leuven, Belgium
Infect Immun; 30(2):513-522 1980

In mice given single ip doses of interferon, serum interferon levels peaked at 1 hr postinjection and were reduced to zero at about 8 hr. The interferon concentrations in spleen, liver, and lungs were about 100-fold higher than could be expected from the amount of serum contained in these organs. In the brain only low levels of antiviral activity were detected. In mice infected ip with Mengo virus, viral replication in the brain occurred around day 4 and was accompanied by the appearance of large amounts of interferon (approx 10(3.25) U/g). This was preceded, however, by viral replication in the spleen and by the appearance of modest amounts of interferon in spleen and serum. In these mice protection could be obtained with relatively small doses of interferon, provided they were given before the time of maximal levels of endogenous serum interferon. In mice infected intranasally with vesicular stomatitis virus, virus replication in the brain started within 24 to 48 hr and increased with time; also, small amounts of interferon (10(2) to 10(2.5) U/g) were already detectable on days 1 and 2. The major peak of virus replication in the brain occurred on days 5 to 6 and was accompanied by the appearance of large amounts of interferon (approx 10(3.25) U/g). In this model early treatment with interferon also provided protection, but only if given in larger doses than in the Mengo virus system. Athymic (nu/nu) mice developed a chronic systemic infection when inoculated with a dermotropic strain of vaccinia virus. No interferon was detected in sera, livers, spleens, or lungs of these animals; some mice had low levels of interferon-like antiviral activity in the brain, but no attempt was made to characterize this material. Daily administration of large doses of interferon failed to exert an effect on the development of this chronic disease. Yet, normal (NMRI) mice were protected against acute infection with dermotropic or neurotropic strains of vaccinia virus, and athymic mice were partially protected against acute lethal infection with neurotropic vaccinia virus. (Author abstract) (22 Refs)

246. ROLE OF INTERFERON IN THE PATHOGENESIS OF VIRUS DISEASES IN MICE AS DEMONSTRATED BY THE USE OF ANTI-INTERFERON SERUM. II. STUDIES WITH HERPES SIMPLEX, MOLONEY SARCOMA, VESICULAR STOMATITIS, NEWCASTLE DISEASE, AND INFLUENZA VIRUSES.

Gresser I, Tovey MG, Maury C, Bandu MT
Institut de Recherches Scientifiques sur le Cancer, Villejuif, France
J Exp Med; 144(5):1316-1323 1976

The role of interferon in the pathogenesis of virus diseases in mice is evaluated. The iv administration of sheep anti-mouse interferon globulin (titer, 4 x 10**-5) resulted in the early appearance of disease and death and increased the overall mortality due to herpes simplex virus (HSV) type I injected either sc or ip. The enhancing effect was most striking when HSV was inoculated sc. Anti-interferon globulin had no effect on the course of influenza A virus infection of mice but resulted in a rapid onset of death in newborn mice infected with Newcastle disease virus and in adult mice inoculated intranasally with vesicular stomatitis virus. When adult mice were treated with the globulin, Moloney sarcoma virus-induced tumors appeared early. The general importance of the early interferon response in host resistance to virus infection is emphasized. (10 refs)

247. APPLICATION OF ANTISERA TO INTERFERON IN STUDYING ONCOGENIC VIRUSES.

Inglot AD, Oleszak E
Lab. Tumor Viruses, Dept. Tumor Immunology, Inst. Immunology and Experimental Therapy, Polish Acad. Sciences, 53-114 Wroclaw, Poland
Arch Immunol Ther Exp (Warsz); 26(1-6):529-536 1978

The effects of sheep anti-mouse interferon (IF) serum on the growth of lesions induced by Moloney sarcoma virus (MSV) and/or herpes simplex virus type 2 (HSV-2) were studied in male BALB/c mice. Anti-IF serum potentiated the growth of MSV-induced tumors, although tumors in all mice regressed spontaneously starting 2 wk after inoculation. After approx 1 mo, all 4-to 5-wk old mice treated with anti-IF serum or untreated were tumor-free. In contrast, in 3-to 4-wk-old mice treated with anti-IF serum, large tumors reappeared at the site of MSV inoculation and metastasized, killing approx 80% of the animals. This metastatic proliferation occurred in only 10% of mice not given anti-IF serum. Anti-IF serum also aggravated the signs of HSV-2-induced ear lesions and increased mortality due to CNS damage following infection. Virus titers in the brain stem and spinal cord were also higher in mice given anti-IF serum. IF protected against HSV-2-induced disease and nullified the enhancing effect of anti-IF serum. Anti-IF serum did not potentiate recurrent HSV-2-induced ear infection or affect apparently healthy mice that had survived HSV-2 infection. Superinfection of Rauscher murine leukemia virus (MuLV-R)-infected mice with HSV-2 inhibited the splenomegaly seen with MuLV-R, and anti-IF serum further amplified this effect. Most mice infected with MuLV-R and HSV-2 died of CNS involvement; anti-IF serum increased the mortality. Mortality due to CNS damage in HSV-2-infected mice was prevented by administration of exogenous IF. (14 Refs)

248. EFFECT OF ANTI-MOUSE TYPE-1 INTERFERON GLOBULIN ON THE EVOLUTION OF MOLONEY SARCOMA VIRUS INDUCED DISEASE IN MICE.

Inglot AD, Inglot O, Zoltowska A, Oleszak E
Lab. Tumour Virology, Dept. Immunology, Inst. Immunology and Experimental Therapy, Polish Acad. Sciences, Wroclaw, Poland
Int J Cancer; 24(4):445-449 1979

The prolonged administration of potent sheep anti-mouse type-1 interferon globulin (anti-IF IgG) had a marked potentiating effect on Moloney sarcoma virus (MSV) infection in mice. The extent of resistance to the MSV-induced disease was age-related. In 4-wk-old BALB/c mice, anti-IF IgG consistently induced 70%-80% mortality due to the progression of early or late tumors and erythroleukemia, whereas mortality of control mice was significantly lower. The same effect was obtained in 1-yr-old BALB/c mice. However, in 4-wk-old C57BL/6 or 6-wk-old BALB/c mice, anti-IF IgG enhanced only the growth of early tumors but had no effect on their regression. Antigenic stimulation with normal sheep globulin suppressed the growth of early tumors in suckling BALB/c or C57BL/6 mice and enhanced the evolution of late MSV-induced disease in older mice. (12 Refs)

249. ROLE OF INTERFERON IN THE PROTECTIVE EFFECT OF THE DOUBLE-STRANDED POLYRIBONUCLEOTIDE AGAINST MURINE TUMORS INDUCED BY MOLONEY SARCOMA VIRUS.

De Clercq E, De Somer P
Rega Inst. Med. Res., U. Leuven, Belgium
JNCI; 47(6):1345-1355 1971

NMRI mice were given single or repeated injections ip of polyriboinosinic acid and polyribocytidylic acid (poly rI:rC) at various times before and after im challenge with Moloney murine sarcoma virus (M-MSV) to demonstrate the function of interferon in the antitumor effect of poly rI:rC. Repeated injections of poly rI:rC (250 microg/ml preparation) started one day before virus challenge and continued on alternate days thereafter to day 11 inhibited the formation of M-MSV-induced tumors. Poly rI:rC treatment begun one day after M-MSV inoculation and continued on alternate days to the 11th day was also effective in inhibiting the development of MSV tumors. Tumor formation was delayed only if a high virus inoculum (10-2 dilution) was used; but tumor formation was definitely suppressed with a lower virus inoculum (10-2.6 dilution). At ten days after M-MSV challenge (10-2 dilution), 18% of mice given repeated doses of poly rI:rC had developed tumors, while 85% of mice given M-MSV without poly rI:rC had developed tumors. To evaluate directly the function of interferon in the antitumor action of poly rI:rC, the effects of poly rI:rC and of exogenous interferon administration were compared. Tumor growth was markedly inhibited with single doses of poly rI:rC at 5 or 25 microg/mouse injected 12 hr before M-MSV inoculation. At 25 microg/mouse the tumor incidence was significantly reduced in animals receiving either a 10-2 or a 10-2.6 dilution of M-MSV. At 5 microg/mouse, poly rI:rC was only slightly effective in mice given a 10-2 dilution but significantly more active in animals given a 10-2.6 dilution. Exogenous interferon inoculation (200 U, ip) gave an antitumor effect intermediate between the protective effects of 5 and 25 microg/mouse of poly rI:rC. Results are thought to indicate that the whole antitumor effect of a single dose of poly rI:rC, injected at 12 hr before M-MSV, is due to interferon production.

250. INHIBITION OF ONCOGENICITY OF MURINE SARCOMA VIRUS (HARVEY) IN MICE BY INTERFERON.

Berman LD
Boston City Hosp., Boston, Mass.
Nature (Lond); 227(5265):1349-1350 1970

Two-wk old mice received ip injections of 0.1 ml of Harvey strain murine sarcoma virus, and, in some cases, a subsequent course of interferon injections (0.2 ml for 30 days), to test the effect of interferon administration on tumorigenesis. Interferon treatment produced a marked delay in mortelity, with treated mice surviving for 20 wk postinfection (controls not treated with interferon died within 7 days after infection with the virus). Autopsy of treated and untreated mice revealed the erythroblastic splenomegaly and discrete peritoneal sarcomata characteristic of disease produced by Harvey murine sarcoma virus.

251. TRANSPLACENTAL INTERFERON-MEDIATED EFFECT IN AKR MICE.

Murasko DM, Blank KJ
Dept. Microbiology, Medical Coll. Pennsylvania, Philadelphia, PA, 19129
Virology; 106(1):148-151 1980

This study was designed to determine whether or not exogenous interferon could produce a modification of virus production in the progeny of mice treated with interferon during gestation. Pregnant AKR mice were treated with exogenous mouse interferon and their progeny examined for the presence of endogenous, ecotropic murine leukemia viruses by the XC assay. Interferon treatment inhibited virus production in most of the progeny for at least 1 wk after birth as compared to control mice. The results of this study clearly demonstrate that: (i) treatment of pregnant mice with exogenous interferon mediates a biological effect frequently associated with interferon in their progeny and (ii) the spontaneous production of infectious, ecotropic murine leukemia viruses by AKR mice can be inhibited by treatment during gestation. (Author abstract) (14 Refs)

252. LYMPHOMA DEVELOPMENT FROM TRANSPLANTED MURINE LEUKEMIA VIRUS INFECTED ORGAN CULTURED THYMUSES: INHIBITORY EFFECT OF IN VITRO INTERFERON TREATMENT.

Riesenfeld I, Tufveson G, Alm GV
Dept. Medical Virology, Biomedical Center, Univ. Uppsala, Uppsala, Sweden
Int J Cancer; 25(4):529-534 1980

Thymuses of 14-day-old AKR mouse embryos were infected with Gross murine leukemia virus (MuLV) and then maintained in organ culture for 3 wk. When they were transplanted to 3-wk-old (AKR x C3H)F1 mice, approx 50% of these developed T lymphomas within 3-4 mo. Most (22/23) tumors were of host, F1-hybrid, origin while only one was of donor AKR type. No clear evidence for in vitro MuLV-induced lymphoma cells was therefore obtained. Exposure of MuLV-infected embryonic thymuses to interferon during the organ culture period significantly reduced the incidence of lymphomas in mice receiving such thymus transplants. Interferon also prevented the appearance of detectable numbers of MuLV antigen-containing lymphocytes in infected organ-cultured thymuses. In contrast, despite the use of very high interferon concentrations, no effects were seen on the number of viable thymic lymphocytes, their proliferation or responsiveness to the polyclonal T-cell mitogens concanavalin A (Con A) and leukoagglutinin (LA). Thus, interferon, presumably through an antiviral effect, can limit the MuLV infection in the thymus and its conse-

quence, ie, development of a lymphoma. (Author abstract) (28 Refs)

253. EFFECTIVENESS OF EXOGENOUS MOUSE INTERFERON IN AKR LEUKEMIA.

Roboz JP, Holland JF, Bekesi JG
Dept. Neoplastic Disease, Mount Sinai Sch. Medicine, New York, NY, 10029

Prog Cancer Res Ther; 2:369-379 1977

The effectiveness of exogenous mouse interferon in the prophylactic treatment of murine leukemia virus-infected preleukemic AKR mice and in the therapeutic treatment of AKR mice with spontaneous leukemia was investigated. In 3-mo-old preleukemic mice treated with multiple im injections of 5 x 10 or 5 x 10 units of interferon, there was a significant reduction in viral titers from 2,000 to less than 100. No changes in viral titers were observed in mice treated with saline or mock interferon. All mice treated with mock interferon developed spontaneous leukemia, and less than 10% remained alive at 12 mo of age. AKR mice receiving the highest concentration of interferon every 2nd day still died at the same rate as the control group, but only 5/40 died of leukemia. The remaining animals showed marked signs of organ atrophy and wasting. Changing the injection schedule from every 2nd day to 1x/wk while maintaining the same total dose produced no toxic side effects, reduced the viral titer, and significantly delayed the appearance of primary leukemia. Interferon at doses of 2 x 10 and 2 x 10 units injected im on days 1, 2, 3, 4, 7, 10, and 15 was also of therapeutic value in the treatment of spontaneous leukemia in AKR mice. The effect was dose related both in terms of reduction of leukemic organ wts and prolonged survival duration. The survival of mice receiving 2 x 10 units of interferon was 29.6 +- 5.2 days compared with 24.4 +- 3.8 days for mice receiving 2 x 10 units and 17.6 +- 2.4 days for controls receiving mock interferon. (23 Refs)

254. TREATMENT OF SPONTANEOUS LEUKEMIA IN AKR MICE WITH CHEMOTHERAPY, IMMUNOTHERAPY, OR INTERFERON.

Bekesi JG, Roboz JP, Zimmerman E, Holland JF
Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, New York, NY 10029

Cancer Res; 36(2,Part2):631-639 1976

Treatment of spontaneous leukemia in AKR mice with a variety of modalities is reported. Both neuraminidase (NA)-treated syngeneic leukemic AKR thymocytes and allogeneic E2G leukemia cells were equally effective in delaying the appearance of primary lymphoma in AKR mice ($p < 0.05$). Immunization with NA-treated L1210 leukemic cells or normal AKR thymocytes was ineffective. Immunotherapy of established leukemia (beginning 14 days after diagnosis) with NA-treated spontaneous leukemic thymocytes or allogeneic E2G leukemic cells without prior cytoreductive therapy did not change the survival pattern. Chemotherapy with vincristine (VCR, 0.75 mg/kg on day 0), palmO-ara-C (130 mg/kg on day 3), and 1-(2-chloroethyl)-3-(trans-4-cyclohexyl)-1-nitrosourea (methyl-CCNU, 25 mg/kg on day 7) resulted in an ILS of 180%, but < 7% of animals survived > 100 days. Combination chemotherapy followed by immunization with 2 x 10(7) NA-treated allogeneic E2G leukemic cells injected on six occasions at multiple sites resulted in survival of 30% of treated animals > 120 days. Immunization alone was ineffective. Cytoreductive therapy alone did not significantly alter the viral titer, but chemotherapy and immunotherapy produced a noticeable decrease in the viral titer after the 13th day, and this was still demonstrable at 45 days. The antiviral agent Virazole alone (up to 800 mg/kg) had no demonstrable antitumor effect on established AKR leukemia. Chemotherapy with VCR + methyl-CCNU + cytoxan increased the life span 183%, but chemotherapy followed by Virazole (200 mg/kg x 3) produced an ILS of 280%. Chemotherapy + Virazole produced a decrease in the viral titer that was evident after the 13th day of treatment. Exogenous mouse *interferon* (5 x 10(4) or 5 x 10(5) units x 5 on days 0, 2, 4, 6, and 8) markedly reduced the virus titer from 2,000 to < 100, and this effect persisted for at least 85 days. Mouse interferon also delayed the onset of primary leukemia in AKR mice. At the highest concentration, treated animals died at the same rate as untreated animals, but only 6/20 died of leukemia; the others died with splenic or thymic atrophy. At 7 x 10(4) units x 5, interferon resulted in 45% of animals living at 52 wk, compared to a median life span of 34-38 wk for untreated animals. Only two animals showed signs of organ atrophy at this dose. (47 refs)

255. EFFECT OF MOUSE INTERFERON IN MURINE LEUKEMOGENESIS (MEETING ABSTRACT).

Yokoro K, Hamada K, Yanagihara K, Kajitani T, Kobayashi S
Dept of Pathology, Hiroshima Univ., Hiroshima, Japan

Proceedings of the 38th Annual Meeting of the Japanese Cancer Association held in Tokyo, Japan, September 1979. Japanese Cancer Association, Tokyo, Japan, 321 pp., 1979.

Present study was undertaken to elucidate the etiological role of endogenous type-C viruses in murine leukemogenesis. A continuous administration of mouse interferon was effective in inhibiting the propagation of neonatally-inoculated Gross virus in NIH/Swiss mice, and the development of leukemia in these mice was completely blocked. On the other hand, a similar course of interferon treatment in x-irradiated (C57BL/6J x C3H/He) F1 mice never altered the frequency of leukemia development. The results suggest that the mechanism of radiation-induced leukemogenesis in mice might be distinct from that induced by the potent leukemogenic viruses. (no Refs)

256. CURRENT STUDIES ON THE THERAPY OF EXPERIMENTAL LEUKEMIA.

Chirigos MA
NCI, Bethesda, Md.

Bibl Haematol; 36:278-292 1970

In mice infected with Friend leukemia virus (FLV), treated for 4 d with 6-mercaptopurine ribonucleoside (6-MPR; 100-300 mg/kg), porfiromycin (2.5-10 mg/kg) or glycine mustard (5-10 mg/kg) beginning 3 d after infection, only 6-MPR caused a significant reduction in serum FLV titers at all doses tested; the other agents were significantly effective only at the highest doses. In mice with 20-d-old FLV infections, treated for 5 d with 6-mercaptopurine (6-MP; 50 mg/kg), actinomycin D (AD; 0.075 mg/kg), cytosine arabinoside (araC; 40 mg/kg) or vincristine (VCR; 0.12 mg/kg), the only agents causing significant regression of splenomegaly (which was correlated with hematological remission) were 6-MP and, to a lesser extent, AD. The effects of araC and VCR were transient. In mice infected with FLV or the plasma variant of Moloney sarcoma virus, a 6-dose pretreatment with pyran copolymer (PC; NSC-46015, from d 6 to d 1 before infection) completely inhibited the development of infection, but PC had no effect when admin after infection. Polyinosinic:polycytidylic acid was less effective than PC against FLV or Rauscher leukemia virus, but markedly inhibited the growth of 1-d-old sc transplants of a spontaneous reticulum cell sarcoma (of CDF, hybrid mice) which

was only slightly inhibited by *exogenous interferon* or L-sarcolysin.

257. EFFECT OF EXOGENOUS AND ENDOGENOUS INTERFERON ON THE COURSE OF LEUKEMIA INDUCED IN MICE WITH FRIEND VIRUS.

Sabashvili MK, Furer NM
Cent. Inst. Hemat. Blood Transfus., Moscow
Antibiotiki; 15(1):52-55 1970

Leukemia was induced in BALB/c mice (18-20 g) by ip inj of a cell-free extract from the spleens of mice with Friend leukemia. The development of leukemia, as measured by the wt of the spleens, was significantly inhibited in mice inj ip with exogenous interferon 3 hours before inj of leukemia virus and every day thereafter. This interferon was obtained by inoc of mouse cell line L with Newcastle disease virus. No effect was noted when interferon was inj. 24 hours after admin of leukemia virus and every day thereafter. Development of leukemia was also inhibited by inj of prodigiosan (Pr; 20 microg, ip) 8 hours before inj of Friend leukemia virus (FLV) and every 3 days thereafter. Pr is a polysaccharide isolated from Serratia marcescens, previously noted as a stimulator of endogenous interferon production. Combined admin of exogenous interferon and Pr inhibited development of leukemia more than admin of either alone.

258. THE EFFECT OF HIGH DOSES OF POLY(I)-POLY(C) INDUCED MOUSE L CELL INTERFERON ON RAUSCHER LEUKEMIA VIRUS INDUCED ERYTHRO-LEUKEMIA IN BALB/C MICE.

Hekman RA, Prins ME, Bosveld IJ, Trapman J
(c/o Trapman) Dept. Pathology, Eramus Univ., P.O. Box 1738, 3000 DR Rotterdam, The Netherlands
Int J Cancer; 27(4):493-500 1981

The effect of high doses of poly(I)-poly(C)-induced mouse L-cell interferon on the development of Rauscher murine leukemia virus (R-MuLV)-induced erythroleukemia in BALB/c mice was determined. Female mice, 4 to 5 wk old, were infected with R-MuLV and treated with interferon every 24 hr starting 6 hr after virus inoculation. Under these conditions injections of 3-5 x 10(4) units of interferon caused a partial inhibition of the leukemic process. Daily application of 3 x 10(5) units completely or almost completely inhibited the erythroleukemia. After 14 days of treatment with these high doses of interferon, spleen wt of interferon-treated infected mice were comparable to those of uninfected animals which received only interferon. Also, no Rauscher cells in spleens and livers of R-MuLV-infected interferon-treated animals could be demonstrated and the spleen structure was well preserved in these mice. In interferon-treated infected animals no virus could be detected in the serum as judged from the absence of reverse transcriptase activity in the serum. Moreover, no virus-infected cells could be demonstrated in spleen or liver as deduced from negative immunofluorescence data using anti-p30 and anti-gp70 sera. No virions budding from spleen cell membranes were seen by electron microscopic studies. However, when interferon treatment was stopped the leukemic process was reactivated and all the mice died. In control experiments interferon caused an inhibition of RBC formation and a 50 to 100% enlargement of the spleen. Pharmacokinetic data showed that, after ip inoculation, max amounts of interferon were present in the peripheral blood after 1-2 hr. After 12-24 hr almost all interferon activity had disappeared from the blood. (Author abstract) (27 Refs)

259. THE EFFECT OF HIGH DOSES OF TYPE I FIBROBLAST INTERFERON ON RAUSCHER MURINE LEUKEMIA VIRUS INDUCED ERYTHROBLASTOSIS IN BALB/C MICE (MEETING ABSTRACT).

Hekman RA, Stoof TJ, Bosveld IJ, Trapman J
Dept. Pathology, Erasmus Univ., P. O. Box 1738, Rotterdam, Netherlands
Exp Hematol; 7(Suppl6):145 1979

Interferons possess, by definition, antiviral activity. Besides this, other biological properties have been described, such as effects on cell growth and the immune system. In mice interferons display antitumor action on transplantable and virus induced tumors. There is increasing evidence that interferons represent a heterogeneous population of molecules, and it is unknown whether the different types of interferon have the same mode of action. We investigated the effects of high doses of partially purified mouse interferon on Rauscher murine leukemia virus (R-MuLV) induced erythroblastosis in BALB/c mice. Interferon preparations used in this study have been produced by mouse L-929 cells after induction with polyinosinic polycytidylic acid and diethylaminoethanol-dextran. These preparations comprise at least two different antiviral components, which can be separated by gel filtration. Both components are able to inhibit the production of R-MuLV by JLS-V5 cells. A significant effect on R-MuLV induced erythroblastosis was observed after daily injection of less than 40,000 reference units of the total interferon, starting 6 hr after virus infection, ie the development of the typical Rauscher erythroblastosis was greatly suppressed in the interferon-treated animals. Whether this effect represents antiviral activity, cell growth inhibiting activity, or is caused by a stimulation of the immune system is under investigation. Moreover, data are presented on the influence of interferons on short term cultures of isolated virus producing Rauscher erythroblasts. (no Refs)

260. ENHANCEMENT OF LEUKEMOGENESIS IN MICE AFTER PROLONGED ADMINISTRATION OF ANTI-INTERFERON OR NORMAL RABBIT GLOBULIN.

Inglot AD, Chudzio T
Polish Acad, Science, Ludwik Hirszfeld Inst. Immunology and Experimental Therapy, ul. Czersha 12, 53-114 Wroclaw, Poland
Arch Virol; 55(1/2):67-75 1977

The prolonged administration of rabbit antimouse L-cell interferon globulin markedly potentiated Rauscher murine leukemia virus (MuLV) infection in BALB/c mice, as shown by spleen size. Normal rabbit globulin had a weaker, but still significant, augmenting effect on spleen enlargement. It was possible to discriminate quantitatively between the nonspecific enhancement of splenomegaly in MuLV-infected mice due to antigenic stimulation with normal rabbit globulin and the effects due to elimination of endogenous interferon by specific antibodies. The difference in spleen-enlarging activity between the anti-interferon IgG and normal rabbit IgG was max 3-4 wk after infection, when potent, diluted anti-interferon IgG (58 ug protein/dose) was used. Endogenous interferon, even when produced in undetectable amounts, apparently plays an essential role in controlling infection by an oncogenic virus. (21 Refs)

261. STUDY OF MECHANISMS OF STIMULATING EFFECT OF RAUSCHER LEUKEMIA VIRUS ON TOGAVIRUS REPRODUCTION IN BALB/C MICE.

Pogodina VV, Malenko GV, Levina LS, Karmysheva VIa, Farutina LM
Inst. Poliomyelitis and Virus Encephalitis, Moscow, USSR
Vopr Virusol; (4):449-454 1980

Mechanisms of stimulating effect of Rauscher leukemia virus (RLV) on the course of togavirus (TV) infections were studied in BALB/c mice. Mice were infected with RLV alone or in combination with TV. The level of splenomegaly was monitored for 8 wk. Presence of virus antigen and identification of togaviruses in lymphocytes of infected mice were tested by the method of fluorescent antibodies. The *interferon* (IF) level in blood sera and spleen extracts was determined on days 1, 3, 7, 10, and 14 after TV infection. TV administration 2 days prior to or simultaneously with RLV inhibited leukemia development, whereas TV administration 2, 7, or 12 days after RLV stimulated leukemia. Double infection with 7-12-day intervals stimulated TV reproduction in internal organs, including the spleen. RLV had more pronounced inhibitory effect on the level of circulating hemagglutinins, as compared with the level of virus-neutralizing antibodies and IF level. (5 Refs)

262. EFFECT OF INTERFERON ON PRODUCTION OF MINIMAL FORMS OF RAUSCHER LEUKEMIA VIRUS IN VIRUS-PRODUCING CELL SYSTEMS.

Soloviev VD, Tatarinova YuI, Balandin IG, Parfenova TM
N. F. Gamaleya Inst. Epidemiology and Microbiology, Moscow, USSR
Dokl Akad Nauk SSSR; 237(1):218-219 1977

To determine the mechanism of the inhibitory effect of interferon (IF) on the development of oncogenic virus-induced leukemias in mice, two leukogenic cell lines (KML-3 obtained from bone marrow of BALB/c mice with Rauscher leukemia, and KML+LB line obtained from healthy BALB/c mice and inoculated on the ninth passage with Rauscher leukemia virus) were incubated with or without IF (20 IU/ml). Virus-containing incubation fluids were then injected ip (0.5 ml) into BALB/c mice. Both KML-3 and KML+LB cells produced leukemia-inducing virus. All mice in the non-IF groups developed leukemia; av duration of survival was 35 days and 41 days, respectively, for mice injected with KML-3 and KML+LB fluids. Inoculation of BALB/c mice with KML-3 and KML+LB cells exposed to IF increased av duration of survival (66 days and 60 days, respectively); and only 14/20 mice and 16/20 mice, respectively, developed leukemia. Assessment of the content of minimal forms of oncovirus showed that exposure to IF significantly elevated production of minimal forms. These findings confirm the hypothesis that IF affects the synthesis of virion components rather than virus escape from the cell. (9 Refs)

263. THE ROLE OF TUMOUR-SPECIFIC ANTIBODY AND INTERFERON PRODUCTION IN THE PATHOGENESIS OF RAUSCHER LEUKAEMIA.

Toth FD, Vaczi L, Balogh M
U. Med. Sch., Debrecen, Hungary
Acta Virol (Praha); 18(1):57-64 1974

The relationship between resistance to Rauscher virus, tumor specific antibody production, and the interferon response was studied in Balb/c, DBA/1, C57Bl/10Sn, (DBA/1 X Balb/c)F1, and (DBA/1 X C57Bl/10Sn)F1 mice. I.p inoculation of the virus (0.2 ml) in the Balb/c mice was followed by a rapidly progressing splenomegaly, all the animals succumbing within 40 days. The spleens of the C57Bl/10Sn mice displayed only very slight enlargement, which was followed by remission starting after the second wk; none of these animals died. The spleen wt of the DBA/1 mice increased to values between those of the other two strains by the third week; this was followed by transitory, partial remission, after which the leukemia progressed again. Most of these animals died during the second exacerbation. Antibodies in the sera of the Balb/c mice never reached significant levels, those in the sera of the C57Bl/10Sn mice increased rapidly and persisted at very high levels, and those in the sera of the DBA/1 mice reached lower maxima and gradually decreased after the 40th day. Rauscher virus was a weak interferon inducer in the Balb/c and C57Bl/10Sn mice, but was a strong inducer in the DBA/1 animals. (DBA/1 X Balb/c)F1 hybrids resembled the Balb/c parents in the rate of splenomegaly and the DBA/1 parents in the course of the leukemia, the tumor-specific antibody production being similar to the more resistant parental strain; interferon production resembled that in the Balb/c mice. The (DBA/1 X C57Bl/10Sn)F1 hybrids reacted similarly to the C57Bl/10Sn parents, except in the interferon response, which resembled that of the DBA/1 parents. Neither the sex of the animals nor the direction of crossing affected the results. Resistance to Rauscher virus infection appears to parallel the rate of tumor-specific antibody production.

264. SEVERITY OF LYMPHOCYTIC CHORIOMENINGITIS VIRUS DISEASE IN DIFFERENT STRAINS OF SUCKLING MICE CORRELATES WITH INCREASING AMOUNTS OF ENDOGENOUS INTERFERON.

Riviere Y, Gresser I, Guillon JC, Bandu MT, Ronco P, Morel-Maroger L, Verroust P
Institut Pasteur, Paris, France
J Exp Med; 152(3):633-640 1980

The severity of disease (ie, impaired growth, delay in organ maturation, liver cell degeneration, and death in the first few wk of life) observed in suckling mice injected at birth with lymphocytic choriomeningitis (LCM) virus depends on the mouse strain; experiments were carried out to determine whether variations in the severity of disease are related to the amount of endogenous interferon (IF) or to a different sensitivity to endogenous IF. BALB/c mice were relatively unaffected by LCM; they grew almost as well as uninfected mice, they had only minimal liver lesions, and none died. Virus-infected C3H mice grew poorly, had extensive liver cell degeneration, and all died. An intermediate pattern was observed in Swiss mice (36% mortality). Despite similar titers of virus in the plasma and liver of all three mouse strains, the amount of endogenous IF produced and the duration of interferonemia differed in these three strains. BALB/c mice produced small amounts of IF detectable in the plasma mostly on day 3 postinoculation. Swiss mice produced more IF detectable on days 3 and 4. C3H mice produced the largest amounts of IF, and interferonemia lasted between days 3 and 6 postinoculation. A marked decrease in the mortality incidence of virus-infected C3H mice was observed when they were injected with a potent anti-mouse IF globulin. Also, the relative resistance of BALB/c mice to LCM disease was not caused by insensitivity to IF action, because exogenous IF inhibited their growth and induced liver lesions comparable to LCM disease. It is concluded that endogenous IF is largely responsible for the manifestations of LCM disease in suckling mice. (17 Refs)

265. CHANGES IN HEMOPOIESIS DURING THE COURSE OF ACUTE LCM VIRUS INFECTION IN MICE.
Bro-Jorgensen K, Knudtzon S
Inst. Medical Microbiology, Univ. Copenhagen, Juliane Maries Vej 22, 2100 Copenhagen O, Denmark
Blood; 49(1):47-57 1977

The function of hemopoietic cells in the course of acute lymphocytic choriomeningitis (LCM) virus infection was investigated in C3H/Sscl mice inoculated with 10(3) mean intracranial lethal doses (LD50) of the virus. During the first week of the infection, there was profound suppression of pluripotential stem cell (CFU) and in vitro colony-forming cell compartments and of 59Fe uptake into the hemopoietic tissues. Enhanced activity of colony-stimulating factor, lack of responsiveness to erythropoietin, and appreciable titers of interferon in the blood and spleen were also noted. After the 10th day, there was a striking increase in CFU and 59Fe uptake confined to the spleen and blood. Restoration of bone marrow, however, was delayed markedly. In late stages of infection and in persistently infected mice, no interferon activity was found. Pretreatment of mice with 850 R of x-rays before injection of LCM virus did not interfere with the amounts of interferon produced. It is suggested that *interferon is the comprehensive suppressor of the hemopoietic precursor cells in the first stage of acute LCM virus infection* and that these cells in the recovery period are directed into erythropoiesis. (35 Refs)

266. PROTECTION AGAINST JAPANESE ENCEPHALITIS VIRUS IN MICE AND HAMSTERS BY TREATMENT WITH CARBOXYMETHYLACRIDANONE, A POTENT INTERFERON INDUCER.
Taylor JL, Schoenherr C, Grossberg SE
(c/o Grossberg) Dept. Microbiology, Medical Coll. Wisconsin, P. O. Box 26509, Milwaukee, WI, 53226
J Infect Dis; 142(3):394-399 1980

A low-mol-wt chemical inducer of interferon, 10-carboxymethyl-9-acridanone (CMA), effectively prevented death caused by Japanese encephalitis virus (JEV) injected peripherally into weanling mice and baby hamsters. Marked reductions in mortality were seen in mice when a single dose of CMA was administered ip, sc, or im to animals challenged ip with JEV. The degree of protection was dependent on dose and time of administration of CMA in relation to virus challenge: all hamsters given CMA on the same day as JEV survived, with lesser although still significant protection when CMA was given 1 or 2 days after JEV. Viremia, an important characteristic of the pathogenesis of natural JEV infection, was reduced nearly 10,000-fold in hamsters treated with CMA. Thus, in the experimental animal models developed for these studies, CMA provided marked therapeutic and prophylactic effect against JEV. (Author abstract) (16 Refs)

267. PERSPECTIVES IN THE CONTROL OF VIRAL DISEASES INCLUDING CANCER.
Hilleman MR
Merck Inst. Ther. Res., West Point, Pa.
Adv Exp Med Biol; 31:167-178 1972

Within a general discussion on the control of viral diseases, the author briefly summarizes studies on interferon and polyinosinic:polycytidylic acid, discusses the significance of the development of Marek's herpes virus disease vaccine as it relates to vaccine development in general, and stresses the importance of establishing criteria of safety and protective efficacy for the eventual application of cancer virus vaccines in man. (no refs)

C.
Antiviral Efficacy of Interferons In Vitro

268. INTERFERON AND BK PAPOVAVIRUS - CLINICAL AND LABORATORY STUDIES.
Cheeseman SH, Black PH, Rubin RH, Cantell K, Hirsch MS
Dept. Medicine, Massachusetts General Hosp., Boston, MA
J Infect Dis; 141(2):157-161 1980

The effects of human WBC interferon on BK papovavirus (BKV) infection in 41 recipients of renal transplants were studied as part of a randomized, double-blind, placebo-controlled trial. Eight transplant recipients demonstrated fourfold or greater rises in antibody to BKV, and three excreted BKV in urine. Neither seroconversion nor excretion was reduced by interferon administration. No clinical syndromes could be clearly linked to BKV infection. BKV was also relatively resistant to the in vitro effects of interferon. Pretreatment of interferon-sensitive human fibroblasts with up to 620 units of interferon/ml resulted in a loss of viral infectivity of one log or less. Continuous exposure of infected cultures of these interferon levels reduced BKV titers by 1.5-2.9 logs, whereas continuous exposure to lower concentrations of interferon has lesser effects. The levels shown to be marginally effective in vitro were considerably higher than those achieved in these patients' sera. (Author abstract) (15 Refs)

269. EFFECT OF INTERFERON ON SOME ASPECTS OF TRANSFORMATION BY POLYOMA VIRUS.
Taylor-Papadimitriou J, Stoker M
Imperial Cancer Res. Fund Lab., London, England
Nature (Lond); 230(12):114-117 1971

Interferon inhibited *polyoma virus-stimulated DNA synthesis* in BHK cells in medium containing only 0.8% serum by 67%; this inhibition was not due to interferon blocking of stable transformation since only 0.03% of serum-deprived cells became stably transformed with the dose of virus used. Interferon had no inhibitory effect on serum-stimulated DNA synthesis. Formation of colonies of 8 cell equivalents or larger in methyl cellulose suspension cultures were inhibited 60-70% by exposure to interferon. The development of random orientation of transformed cells in monolayer cultures in conditions of serum depletion was also inhibited by interferon. The initial development of several characteristics of polyoma-transformed cells seemed to be inhibited by interferon irrespective of whether these characteristics were abortive or stably inherited, although no inhibitory effects were seen once stable transformation was achieved. Stable transformation was thought to involve integration, and an interferon-sensitive viral gene may be required for this event, or integration may modify viral gene products required for the expression of the transformed cell phenotype so that they become insensitive to interferon.

270. THE DIFFERENTIAL EFFECT OF INTERFERON ON T ANTIGEN PRODUCTION IN SIMIAN VIRUS 40-INFECTED OR TRANSFORMED CELLS.
Mozes LW, Defendi V
Papanicolaou Cancer Res. Inst., 1155 N.W. 14th St., Miami, FL, 33101
Virology; 93(2):558-568 1979

The ability of interferon (IF) to inhibit tumor antigen (T Ag) production in simian virus 40 (SV40)-infected or -transformed cells was studied primarily through the use of immunoprecipitation followed by gel electrophoresis and autoradiography. Addition of IF to monkey cells prior to or subsequent to inoculation with SV40 inhibited the amount

of T Ag that was synthesized late in infection. In contrast, when a similar experiment was performed with a temperature-sensitive mutant of SV40, tsA58, which does not replicate at the nonpermissive temperature, the amount of immunoprecipitable T Ag was not inhibited when IF was added at 30 hr postinfection at 40.5 C. The effect of IF on an integrated vs nonintegrated genome within the same cell population was studied in an SV40-transformed mouse cell line, H6-15, which is temperature-sensitive for the transformed phenotype and for the expression of T-antigen. In shift-down experiments, the reappearance of SV40 T Ag was insensitive to the addition of IF, whereas superinfection of H6-15 cells with polyoma virus resulted in a dose-dependent inhibition of polyoma T Ag infection. An SV40-transformed mouse cell line (nonpermissive) and two SV40-transformed human cell lines (semipermissive) were passaged in the presence of IF for four generations. Approx the same amount of labeled T Ag could be immunoprecipitated from IF-treated compared with control mouse cultures, whereas there was a marked decrease in the amount of newly synthesized T Ag in IF-treated human cultures. All these results are compatible with the hypothesis that IF affects differentially the expression of early viral genes whether the viral DNA is integrated or not integrated. (34 Refs)

271. BIOLOGY OF SIMIAN VIRUS 40 (SV40) TRANSPLANTATION ANTIGEN (TRAG). IV. INHIBITION BY HUMAN INTERFERON OF EXPRESSION OF SV40 TRAG IN SV40-INFECTED MONKEY CELLS.

Tevethia SS, Greenfield RS, Rieder V, Tevethia MJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Virology; 95(2):587-592 1979

Treatment of African green monkey kidney cells with human interferon prior to simian virus 40 (SV40) infection inhibited the expression of SV40 transplantation antigen (TrAg) as well as tumor (T) antigen. The inhibition occurred in SV40-infected but not in SV40-transformed monkey cells. The synthesis of SV40 T antigen as detected in the indirect immunofluorescence test and of large and small T antigens as detected by immunoprecipitation with sera from tumor-bearing hamsters and electrophoresis in sodium dodecyl sulfate-gels was similarly affected in SV40-infected monkey cells. These results suggest that the induction of SV40-specific TrAg in the cytolytic cycle depends upon a viral, rather than a host, message. (26 Refs)

272. T-ANTIGEN EXPRESSION IN HUMAN SKIN FIBROBLASTS IS NOT REGULATED BY AN ENDOGENOUS INTERFERON RESPONSE TO SV40 INFECTION. BRIEF REPORT.

Lubiniecki AS, Blattner WA, Cruttenden V, Gunnell M, Tarr GC, Fraumeni JF
Life Sciences Div., Meloy Lab., Inc., Springfield, VA
Arch Virol; 57(4):349-354 1978

Exogenous interferon may affect simian virus (SV)40 T-antigen expression, depending on the chromosomal complement, time of treatment, and biological factors in human cells. However, no evidence was found for endogenous interferon response to SV40 infection in the regulation of T-antigen expression. (Author abstract) (22 Refs)

273. REGULATION OF PROLIFERATION OF SV40-TRANSFORMED CELLS.

Hirano A
Dept. Virology, Tottori Univ. Sch. Medicine, Yonago-shi, Tottori Prefecture 683, Japan
Yonago Igaku Zasshi; 29(4):340-349 1978

Cytochalasin B, a metabolite from the mold Helminthosporium dematioidem, inhibits cytoplasmic division of normal cells and Simian virus (SV)40-transformed cells at a concentration of 1 ug/ml. In the presence of cytochalasin B at this concentration, normal cells became bi- or trinucleated. In SV40-transformed cells, the number of nuclei per cell increased significantly, and cells with 5-10 nuclei were frequently observed. Multinucleation of SV40-transformed cells was reduced in the presence of dibutyryl cyclic AMP, *interferon* or polyinosinic polycytidylic acid. Upon removal of cytochalasin B, cytoplasmic division recovered rapidly, and consequently mononucleate cells were formed. The majority of resulting mononucleate cells in transformed cells cannot divide further, and the ability to form colony or tumor was reduced. Besides the difference in multinucleation, differences in response to cytochalasin B between normal cells and transformed cells were also observed in DNA synthesis or thymidine kinase activity. DNA synthesis and thymidine kinase activity of normal cells were inhibited by cytochalasin B, but this was not the case in transformed cells. From these different reactions of these cells to cytochalasin the presence of different proliferation control mechanisms was suggested. (Author abstract) (23 Refs)

274. EFFECT OF INTERFERON ON SERINE PROTEASE ACTIVITY OF SIMIAN VIRUS 40 TRANSFORMED 3T3 (SV3T3) CELLS (MEETING ABSTRACT).

Schroder EW, Chou IN, Black PH
Dept. Medicine, Massachusetts General Hosp., Boston, MA, 02114
J Cell Biol; 79(2,part2):75a 1978

The effect of semipurified mouse fibroblast interferon (IF) on the activity of a serine protease, plasminogen activator (PA), in SV3T3 cells has been investigated. Plasminogen dependent degradation of an 125I-fibrin substrate was used to measure PA activity. Pretreatment of SV3T3 cells for 18-24 hr with 50-100 NIH units of IF/ml resulted in a 40-55% reduction in the PA released into serum free medium collected after 10-12 hr. Cell associated PA activities of Triton X-100 cell lysates were not significantly reduced. The doses of IF used did not affect the assay procedure. Treatment of IF with antiserum, or by heating, caused parallel reductions in the inhibition of PA release and in the antiviral effect. Dialysis of IF did not affect either activity. These controls indicate that IF is responsible for the observed activity. Treatment of SV3T3 cells with up to 500 units of IF/ml did not affect the incorporation of 3H-amino acids into protein. Also, IF did not affect the increase in cell associated PA activity which occurred after changing SV3T3 cells to serum-free medium. The doses of IF used did inhibit the growth of SV3T3 cells by 15-20%. We conclude that IF inhibits the release of PA from SV3T3 cells by a mechanism which is not dependent upon decreased synthesis of PA. The IF effect may result either from a direct action on the release of PA from the cell surface, or from an indirect effect related to inhibition of cell proliferation. Similar mechanisms could be important in other IF-mediated alterations of cellular properties, particularly those which may involve decreased release of macromolecules such as H-2 antigens and also of C-type virus from the cell surface. (no Refs)

275. INHIBITION OF ADENOVIRUS TYPE 2 BY HUMAN AND MONKEY INTERFERON (MEETING ABSTRACT).

Henry CJ, Slifkin M
Allegheny Gen. Hosp., Pittsburgh, Pa.
Proc Soc Exp Biol Med; 137(4):1432-1436 1971

A study performed to determine the extent to which monkey and human interferon inhibit adenovirus type 2 (Ad 2) growth in Vero monkey cells and in human embryonic fibroblasts is reported. Monkey interferon is more effective in inhibiting Ad 2 antigen synthesis and virion formation than is human interferon. The effect of a single dose of interferon on the growth of Ad 2 was determined; Vero cells and human embryonic kidney cells were treated with either monkey or human interferon, resp. Cultures were subsequently infected with Ad 2, and the effect of the two interferons on Ad 2 replication was observed. Monkey interferon reduced Ad 2 growth in Vero cells by about 95% at 90 hr postinfection; human interferon reduced infectious virus growth by 50-60% at 70 hr postinfection in human cells. Interferon inhibition of Ad 2 capsid antigen formation in human and monkey cells was also investigated. Monkey interferon inhibited Ad 2 antigen formation by 96-98% in Vero cells, while human interferon inhibited Ad 2 antigen formation by 65-80% in human embryonic kidney cells. Both monkey and human interferon reduced the number of cells showing positive fluorescence in homologous cell cultures. Results suggested that some serotypes of human adenoviruses were sensitive to interferon from animals other than their natural hosts.

276. PRODUCTION OF HEPATITIS B SURFACE (HBS) ANTIGEN BY HUMAN HEPATOMA CELL LINES IN CULTURE (MEETING ABSTRACT).

Huh N, Utakoji T
Dept. Cell Biology, Cancer Inst., Japanese Foundation Cancer Res., Toshima-ku, Tokyo 170, Japan
Proceedings of the 39th Annual Meeting of the Japanese Cancer Association held in Tokyo, 5-7 November, 1980. The Japanese Cancer Association, Tokyo 170, Japan, 367 pp., 1980.

To elucidate the role of hepatitis B (HB) virus in human B type hepatoma and hepatocellular carcinoma, cell lines were established from four hepatoma patients with and without HBs antigen, and examined for production of HBs antigen. Two cell lines derived from HBs antigen carriers (huH-1, huH-4) produced HBs antigen in culture continuously. This was shown immunologically by reversed passive hemagglutination and radioimmunoassay, and morphologically by immunoelectron microscopy. The two cell lines derived from non-HBs carriers (huH-2, huH-3) did not produce HBs antigen. The HBs-antigen production of huH-1 was increased by the addition of dexamethasone, the increase was dose dependent and the HBs antigen increased about 10-fold at the optimum concentration of 10(-6)-10(-5) M. The addition of dexamethasone did not affect protein synthesis or RNA synthesis. The production of HBs antigen by huH-1 was also increased by the addition of dibutyl cyclic AMP (But2cAMP) (4-fold with 1 milliM) and in the presence of both But2cAMP and dexamethasone the increase was synergistic. The production of HBs antigen by huH-4 was little affected by the addition of dexamethasone. The production of HBs antigen by huH-1 was inhibited by *interferon* derived from human WBC at a concentration that did not greatly affect the syntheses of protein or RNA. The regulatory mechanism of HBs-antigen production in the presence or absence of a dexamethasone receptor is discussed on the basis of these results. (no Refs)

277. FATE OF INTERFERON-TREATED CELLS.

Friedman RM, Costa JR
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, Digestive Diseases, NCI, Bethesda, MD 20014
Infect Immun; 13(2):487-493 1976

Cultures of Ly cells were treated with interferon (100 units/ml) 24 hr prior to infection with vesicular stomatitis virus (VSV). After 1 day, virus titers in the culture began to fall, and they reached approx 10(3) TCID50 by the seventh day. Thereafter, titers again rose and reached 10(5) TCID50 by day 14, at which time all cells in the culture showed a viral cytopathic effect (CPE). When interferon was added to the medium on days 4 and 6 as well as 1 day before infection, the virus titer fell to < 10 TCID50 by day 12. Subsequently, virus titers increased to almost 10(7) log10 TCID50 by day 18, at which time the culture was destroyed. When interferon was added on days 9, 11, and 15, there was a rapid decrease in virus titer; by day 12 the titer was < 10 TCID50 (undetectable), and it remained at this low level for at least 35 days. These cultures were considered cured. Several methods, including cocultivation and molecular hybridization, failed to demonstrate the persistance of a significant portion of the VSV genome in these cultures. In Ly cells treated with interferon (1,000 units/ml) and then infected with herpes simplex virus (HSV) at a multiplicity of 10, approx 40% of the monolayer was severely damaged by the virus after 18-24 hr. In control cultures not treated with interferon, the cytopathology was greater. In interferon-treated cultures, slow cell growth began 2-3 days after infection, and by day 4 a sufficient number of cells was present to split the monolayer after trypsin treatment. HSV titers were reduced by 10(3)-fold after 24 hr, and the steadily declining virus titer reached undetectable levels by day 5. HSV antigens were demonstrated in nearly all control virus-infected cells after 8 and 24 hr of infection. In the interferon-treated cultures, 82% of cells were HSV antigen-positive at 8 hr, 44% were positive at 24 hr, and no HSV antigens could be detected thereafter. (16 refs)

278. SELECTIVE ANTIVIRAL ACTIVITY OF HUMAN INTERFERONS ON PRIMATE ONCOGENIC AND NEUROTROPIC HERPESVIRUSES.

Daniel MD, Tamulevich R, Bekesi JG, King NW, Falk LA, Silva D, Holland JF
New England Regional Primate Res. Center, Harvard Medical Sch., Southboro, MA, 01772
Int J Cancer; 27(1):113-121 1981

Human lymphoblastic interferon, leukocytic interferon, and fibroblastic interferon were found to have marked antiviral activity on the replication of Herpes virus saimiri and Herpes virus ateles when used at a concentration of 500 IU/ml or greater but only minimal activity against two neurotropic viruses, viz Herpes virus platyrrhine and herpes simplex virus. All three interferons were equally effective as antiviral agents against the oncogenic herpesviruses. Pretreatment of cells with interferons before virus infection was not required as it failed to enhance or retard the antiviral action of interferon, particularly in the case of the oncogenic herpesviruses. The moi of virus ranging from 100 to 0.0002 did not alter the effectiveness of the antiviral ability of interferon which was maintained at these virus concentrations. Interferon was equally effective in suppressing the replication of the two oncogenic viruses at low and high moi (20 to 0.00002). Interferon was able to suppress the advancement of virus-induced cell cytopathic effect of HVS- and HVA-infected cell monolayers. This event could be repeated continuously over a period of several mo by addition and withdrawal of interferon. Virus-infected cell mono-

layers exhibiting advance (75%) of cell cytopathology could be treated with 10,000 IU/ml interferon to attain cell confluency. These treated cells subsequently could be subcultivated (if maintained on 2,000 IU/ml interferon) for over 14 mo and 20 subpassages with an absence of virus, viral antigens, or virus particles. These same cells, if maintained in the absence of interferon during each subpassage level, will produce virus; however, from the 14th subpassaged cell cultures virus appears to have been repressed or lost in the absence of interferon, suggesting that long-term application of interferon may have a therapeutic effect in 'eliminating' virus infection. Owl monkey kidney cells infected with HVS or HVA at a moi of greater than 1 (2 and 20) or moi less than 1 (to induce a multicycle infection) were successfully treated with interferon. (Author abstract) (34 Refs)

279. COMPARATIVE STUDIES OF INTERFERON AND THREE ANTIVIRAL AGENTS ON NEUROTROPIC AND ONCOGENIC HERPESVIRUSES.

Daniel MD, Falk LA, King NW, Tamulevich R, Holland JS, Bekesi JG
New England Regional Primate Res. Center, Harvard Medical Sch., Southborough, MA, 01772
Antimicrob Agents Chemother; 18(4):622-628 1980

The antiviral effects of four compounds, phosphonoacetate, phosphonoformate, acycloguanosine, and purified human lymphoblastic interferon, were tested against two neurotropic herpesviruses, herpesvirus platyrrhine and herpes simplex virus, and two oncogenic herpesviruses, herpesvirus saimiri and herpesvirus ateles. All four compounds induced different degrees of inhibition of these herpesviruses. Phosphonoacetate and phosphonoformate at concentrations of 50 ug/ml or greater showed powerful antiviral activities. Interferon was more effective against herpesvirus saimiri and herpesvirus ateles, the two oncogenic viruses. Herpes simplex virus and the oncogenic herpesviruses were effectively inhibited by acycloguanosine, whereas herpesvirus platyrrhine proved to be resistant. The simian herpesviruses required a higher concentration of phosphonoformate, phosphonoacetate, and acycloguanosine for antiviral action. The antiviral action of all four compounds was contingent on the continued presence of the compounds in the infected cell culture medium. (Author abstract) (23 Refs)

280. INHIBITORY EFFECTS OF ACYCLOGUANOSINE (AG) AND HUMAN LYMPHOBLASTOID INTERFERON (IF) ON HERPESVIRUS SAIMIRI (HVS) AND HERPESVIRUS ATELES (HVA) (MEETING ABSTRACT).

Daniel MD, Tamulevich R, Silva D, Bekesi G, Holland J, King N, Falk L
New England Regional Primate Res. Center, Harvard Medical Sch., Southboro, MA, 01772
Proc Am Assoc Cancer Res; 20:233 1979

Acycloguanosine (AG) and human lymphoblastoid interferon (IF) were evaluated for antiviral activity against two oncogenic viruses, HVS and HVA. AG at concentrations of 0.5-200 uM were employed against 100-10,000 median tissue culture infective dose (TCID50) of HVS and HVA; 3.0 uM was the lowest AG concentration to produce antiviral effects. AG at 200 uM concentration inhibited 1,000 TCID50 of HVA but not HVS. This inhibition was reversible when the drug was removed. HVA transformed rabbit lymphoblastoid cells failed to proliferate in the presence of 50 uM AG and cell counts dropped from 2.2 x 10(6) to 5.6 x 10(5) in 25 days. Virus could still be recovered from these cells. These cells tolerated 1,000 units of IF during a period of 70 days but IF failed to stop replication of virus in these cells. IF at concentrations of 1,000 and 2,000 units had antiviral activity against HVS and HVA in owl monkey kidney cells but this effect was also reversible. In immunofluorescence studies early and late antigen expression was inhibited in AG and IF treated cell cultures, but developed after the removal of the drugs. Electron microscopic studies of AG and IF treated cells when compared to controls revealed no morphological differences between the two groups. It could be concluded that both AG and IF have antiviral activity against HVS and HVA but this activity is contingent on the continued presence of the drugs. The action of both drugs seems to be virostatic and not viruscidal. (no Refs)

281. INTERFERON IN THE REPLICATION OF HERPES SIMPLEX VIRUS IN NORMAL AND PATHOLOGICAL NERVE CELLS.

de la Pena NC, Bal E, Puricelli L, Diaz A, De Lustig ES
Res. Dept. Inst. Oncology Angel H. Roffo, Buenos Aires Univ., Buenos Aires, Argentina
IARC Sci Publ; 24(II):1055-1066 1978

The role of human interferon (HI) and human colostral secretory IgA (S-IgA) in herpes simplex virus (HSV) replication in the nervous system was studied in vitro. When trigeminal ganglia explants from rabbits with experimental herpetic keratitis were infected with HSV type 1 (HSV-1) and treated topically with HI or HI/S-IgA, HSV was recovered from 30% of the ganglia after 15-19 days cocultivation on rabbit kidney (RK 13) cells. A restrictive HSV productive infection was demonstrated in ganglia and nerves of newborn rabbits in organ culture, the yields always being higher in nerve cultures. HI had no direct effect on HSV-1 replication. However, when explants were treated with HI and IgG for 48 hr before and after infection, a delay in the expression of HSV-1 was detected by cocultivation. HSV-1 and HSV-2 replicated in a C1300 murine neuroblastoma clone, the cytopathic effects being more marked for HSV-2 at 24 hr. HSV-specific antigens were demonstrated by the immunoperoxidase technique. (11 Refs)

282. INHIBITION OF HERPES SIMPLEX VIRUS TYPE 2-INDUCED BIOCHEMICAL TRANSFORMATION BY INTERFERON.

Rapp F, Nishiyama Y
Dept. Microbiology and Specialized Cancer Res. Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
J Virol; 33(1):543-546 1980

The effect of interferon on the biochemical transformation of thymidine kinase-deficient cells by UV-inactivated herpes simplex virus type 2 has been studied. Transformation was much less sensitive to the action of interferon than virus multiplication. However, the continuous presence of a high dose of interferon (2,000 units) inhibited transformation almost completely. Although we could not differentiate between the effect of interferon on fixation and expression of the virus thymidine kinase gene, data suggest that the inhibitory effect of interferon on transformation might be partially due to the suppression of virus thymidine kinase expression. (Author abstract) (20 Refs)

283. COMBINED ANTIVIRAL EFFECTS OF INTERFERON, ADENINE ARABINOSIDE, HYPOXANTHINE ARABINOSIDE, AND ADENINE ARABINOSIDE-5'-MONOPHOSPHATE IN HUMAN FIBROBLAST CULTURES.

Bryson YJ, Kronenberg LH
Dept. Pediatrics, Sch. Medicine, Univ. California, Los Angeles, CA 90024

Antimicrob Agents Chemother; 11(2):299-306 1977

Plaque inhibition of vaccinia and herpes simplex type 2 (HSV-2) viruses in cultures of human diploid foreskin fibroblasts (HSF) was used to examine the antiviral activities of human fibroblast interferon, adenine arabinoside (ara-A), hypoxanthine arabinoside (ara-Hx), and adenine arabinoside 5'-monophosphate. For vaccinia virus, the median inhibitory doses of the arabinosides were 0.14 uM of ara-A, 0.22 uM of ara-AMP, and 1.7 uM of ara-Hx. For HSV-2, the median inhibitory doses were 0.67 uM of ara-A, 1.2 uM of ara-AMP, and 57 uM of ara-Hx. In another set of experiments, confluent HSF monolayers were incubated overnight in maintenance medium containing serial three-fold dilutions of human fibroblast interferon. The cultures were then washed, infected with 60 plaque forming units of either vaccinia virus or HSV-2 per culture, and replenished with maintenance medium containing doses of arabinosides chosen to give approx 25% plaque inhibition. By combining doses of interferon and arabinosides that, acting alone, gave intermediate degrees of plaque inhibition, a comparison of the combined antiviral activity with that calculated from the activity of each inhibitor alone was made. The plaque-inhibitory activities of interferon and the arabinosides tested were found to be statistically independent as evidenced by close agreement between the observed and expected results. The results also indicated that the arabinosides do not destabilize the antiviral state previously induced by interferon and that interferon pretreatment does not interfere with subsequent arabinoside action in infected cells. Arabinosides also did not appear to affect the induction of interferon synthesis by either Newcastle disease virus or double stranded RNA, indicating that they are not themselves interferon inducers. (24 refs)

284. MURINE CYTOMEGALOVIRUS: INDUCTION OF AND SENSITIVITY TO INTERFERON IN VITRO.

Oie HK, Easton JM, Ablashi DV, Baron S
Natl. Cancer Inst., Bethesda, MD 20014

Infect Immun; 12(5):1012-1017 1975

To reevaluate the role of interferon during murine cytomegalovirus (MCV) infection in vitro, moderate amounts of interferon were produced by mouse embryo (ME) cultures. The growth studies of MCV in ME cells showed that interferon was produced as early as 4 hr after infection, infectious virus was produced between 12 to 16 hr, and cytopathic effect was produced between 16 to 18 hr. Pretreatment of ME cells with varying concentrations of interferon before infection with MCV did not result in increased interferon production, but at high pretreatment doses a slight inhibitory effect on interferon production was observed. In vitro sensitivity studies showed that small doses of MCV were highly sensitive to the antiviral action of interferon, but higher viral doses proved to be markedly resistant. A small number of interferon-resistant virus-infected cells may account for this.

285. EFFECT OF INTERFERON ON CHRONIC INFECTION OF HUMAN CELLS BY XENOTROPIC TYPE-C VIRUSES.

Peries J, Canivet M, Rhodes-Feuillette A, Todaro GJ
Unite INSERM 107, Institut de Recherches sur les Leucemies, Hopital Saint-Louis, 75010 Paris, France

Int J Cancer; 23(6):798-802 1979

Different preparations of human interferon inhibit virus production in human cells chronically infected by a variety of type-C xenotropic viruses. Some of these viruses have been incriminated in the development of leukemia in primates. The characteristics of blocking of viral multiplication are similar to those described for the effect of mouse interferon on ecotropic viruses. The amount of free virus in culture supernatants is strongly decreased while intracellular protein p30 stays unchanged or is slightly increased. On the other hand, the inhibitory effect is reversible. The withdrawal of interferon results in a rapid increase in virus production as detectable in supernatant fluids. In the light of these results it is suggested that human interferon might be useful in the treatment of some blood malignancies suspected of being related to infection with xenotropic type-C viruses. (Author abstract) (24 Refs)

286. EFFECT OF INTERFERON ON HUMAN CELLS RELEASING ONCORNAVIRUSES: AN ASSAY FOR HUMAN INTERFERON.

Salzberg S, Heller A, Aboud M, Gurari-Rotman D, Revel M
Dept. Life Science, Bar-Ilan Univ., Ramat Gan, Israel

Virology; 93(1):209-214 1979

Human RD-114 cells chronically infected with a feline RNA tumor virus were treated with 20 or 60 units/ml of human interferon (IF) to determine the kinetics of development of the antiviral state in these cells. The amount of virus released was monitored by reverse transcriptase (RT) activity in the culture medium. RT activity was inhibited by 70%-80% 4-6 hr after the cells were treated with 60 units/ml IF. When RD-114 cells were treated with 10 or 60 units/ml IF for 18 hr, the antiviral state remained unaltered at 20 hr after IF removal; with the higher concentration, greater than 70% inhibition in virus release was observed 24 hr postremoval. Human IF and mouse IF showed species specificity when tested for their effects on virus release from RD-114 and mouse NIH/3T3 (murine leukemia virus) cells. Human IF was titrated on RD-114 cells by monitoring the RT activity in the culture medium or by determining the reduction in the number of plaques formed on cell monolayers after infection with vesicular stomatitis virus. Both assays were identical in their sensitivity. The use of the RT assay for detecting human fibroblast IF during its purification by ion-exchange chromatography is illustrated. (18 Refs)

287. EFFECT OF BROMODEOXYURIDINE AND INTERFERON ON CELLULAR AND VIRAL FUNCTIONS IN HUMAN PROSTATIC CELLS.

Chawda R, Job L, Horoszewicz JS, Carter WA, Arya SK
Dept. Medical Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY

Oncology; 36(1):35-39 1979

Some of the human prostatic cells in culture apparently produce oncornavirus-like particles. Bromodeoxyuridine does not enhance the production of these particles. On the contrary, this drug depresses such production. This depression is likely to be due to the cytotoxic effects of bromodeoxyuridine for these cells. These results can be interpreted to suggest that the human prostatic cells used in this study do not contain endogenous oncornavirus genetic information that is

inducible. Purified human *interferon* inhibits the production of oncornavirus-like particles by these prostatic cells. It also inhibits the rate of cellular DNA synthesis in these cells. These results are consistent with the notion that the inhibitory effects of interferon are mediated through its effect on cellular biosynthetic machinery. (Author abstract) (22 Refs)

288. INHIBITION OF MASON-PFIZER MONKEY VIRUS-INDUCED SYNCYTIUM FORMATION IN NORMAL HUMAN CELLS BY HOMOLOGOUS INTERFERON.

Chatterjee S, Hunter E
(c/o Hunter) Dept. Microbiology, Univ. Alabama in Birmingham, Medical Center, Birmingham, AL, 35294
Virology; 104(2):487-490 1980

Pretreatment of human cells with homologous interferon reduces the number as well as the size of the multinucleate cells observed after M-PMV infection. The inhibition observed is species specific since treatment with interferon of rhesus fetal lung cells, which are as susceptible to M-PMV-induced cell fusion as human cells, did not result in any significant reduction in multinucleate cell formation. (Author abstract) (13 Refs)

289. EFFECT OF HUMAN INTERFERON ON THE VIRUS PRODUCTION OF A CELL LINE CHRONICALLY INFECTED WITH TYPE D RETROVIRUS. (MASON-PFIZER).

Rhodes-Feuillette A, Cavalieri F, Canivet M, Peries J
Dept. d'Oncologie Experimentale, Institut Recherches sur les Maladies du Sang, Hopital Saint-Louis, 75475 Paris Cedex 10, France
C R Acad Sci [D] (Paris); 288(16):1239-1241 1979

Viral production in two human cell lines chronically infected with retrovirus (a GaLV derivative and A204 MPV) was measured in the presence of human and mouse interferons. Cell cultures exposed to 200 IU/ml of human interferon for 24 hr showed a greater decrease in production of the type C GaLV virus (82%) than of the type D MPV virus (58%). (7 Refs)

290. INHIBITION BY INTERFERON OF SENDAI VIRUS CYTOLYSIS.

Sato T, Tomita Y, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
Infect Immun; 28(1):6-10 1980

Treatment of HeLa cells with human interferon inhibited 51Cr release from cells induced by UV-inactivated Sendai virus. The inhibitory effect became apparent about 6 hr after interferon treatment and persisted for 24 to 48 hr. In the interferon-treated cells, the cytolysis was inhibited within 10 min after adding virus, and the inhibitory action was suppressed by the treatment of the cells with cycloheximide. Mock interferon and mouse interferon did not inhibit the cytolysis and antiinterferon serum neutralized the effect of interferon. All these findings indicate that Sendai virus-induced cytolysis is inhibited by interferon per se. However, interferon did not have any influence on Sendai virus hemolysis. (Author abstract) (28 Refs)

291. SUPPRESSIVE EFFECTS OF INTERFERON ON SYNCYTIUM FORMATION BY RD-114 VIRUS IN HUMAN TRANSFORMED CELLS.

Tomita Y, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
J Gen Virol; 43(part1):111-117 1979

The RD-114 virus rapidly induced syncytia in the human transformed cell lines, RSa, RSb and IFr. Treatment of the virus with heat or ultrasonic vibration completely eliminated the syncytium-forming activity. Irradiation with UV light or treatment with beta-propiolactone (BPL) reduced but did not completely destroy the activity. Pre-treatment of the cells for 16 hr with 25 to 500 units/ml of human WBC interferon (Le-IF) or fibroblast interferon (F-IF) significantly reduced formation of syncytia by active virus or inactivated (UV or BPL) virus. This activity of interferon was inhibited by treatment of the cells with cycloheximide. Interferon did not increase the binding of 3H-uridine-labeled RD-114 virus to the cells. It is postulated that interferon treatment altered the plasma membrane of the cells and thus reduced their capacity to fuse. (Author abstract) (31 Refs)

292. RAPID ONSET OF THE INTERFERON-INDUCED ANTIVIRAL STATE IN HUMAN NASAL EPITHELIAL AND FORESKIN FIBROBLAST CELLS.

Harmon MW, Greenberg SB, Johnson PE
Dept. Microbiology Immunology, Baylor Coll. Medicine, Houston, TX, 77030
Proc Soc Exp Biol Med; 164(2):146-152 1980

The magnitude and rate of activation of an antiviral state in nasal epithelial (NE) cells after exposure to interferon (IF) were compared with the corresponding rate and magnitude for human foreskin fibroblast (HFF) cells. The antiviral states were detected by reduction of yield of plaque forming units (PFU) from cells exposed to the IF. The mean control vesicular stomatitis virus (VSV) yield from NE cells 24 hr after challenge with the virus was 5.39 +-0.16 PFU/ml (log10), and the corresponding yield for HFF cells was 8.16 +-0.23 PFU/ml (log10). When the cells were exposed to 4-40,000 units IF/ml for 15 min, 1 hr, or 18 hr and then challenged with VSV, both types of cells responded in a time- and dose-dependent manner, although the reduction of VSV yields in the NE cells was less than that in the HFF cells. The slopes of the dose-response curves were 0.9 and 0.3 for the HFF and the NE cells, respectively. It was noted that the antiviral state developed rapidly (15 min) in NE cells exposed to high IF concentrations. The observed reductions in virus yields were not caused by a toxic effect of IF, since no reduction in cell viability was detected. When the sensitivities of coxsackievirus A type 21 (Cox A-21) and parainfluenza virus type 3 (P-3) to the antiviral state in NE cells were compared to that of the VSV, the sensitivity of the Cox A-21 was found to be nearly equivalent to that of the VSV, while the sensitivity of the P-3 was significantly less than that of the VSV. IF preparations obtained from nasal washes (presumably NE cell IF) and from WBC were equally effective in activating an antiviral state in the NE cells. (23 Refs)

293. FUNCTIONAL AND ULTRASTRUCTURAL STUDIES OF THE EFFECTS OF HUMAN INTERFERON ON CELL MEMBRANES OF IN VITRO CULTURED CELLS.

Degre M, Hovig T
Capt. and Mrs. Wilhelmsen's Inst. Bacteriology Rikshospitalet, Oslo 1, Norway
Acta Pathol Microbiol Scand [B]; 84(6):347-358 1976

The effects of human interferon on uninfected and virus-infected human cells were studied by scanning electron microscopy. The U line of human amnion cells was infected with vesicular stomatitis virus (10 TCID50) 6 hr after inoculation with 100 units of human leukocyte interferon. The titer of infectious virus was reduced 2 log units after 18 hr incubation. Interferon inhibition of U-cell growth rate was significant after 3 days of incubation, relative to control rates; inhibition was dose-dependent, with 10 units of interferon/ml decreasing cell numbers by 15% and 100 units/ml by 50%. Interferon inhibition of spontaneous release of ra-

dioactivity after treatment with, and removal of, tritiated uridine was also dose-dependent, up to 10 units/ml; the effect was not increased by increased interferon concentration. No conspicuous difference in growth pattern, cell surface, or cell size or shape was found between control cells and cells after interferon treatment at any concentration, including 2,000 units/ml. The data suggest a membrane-stabilizing role for interferon. (26 refs)

294. INTRINSIC INTERFERENCE: NON-INTERFERON MEDIATED VIRAL INTERFERENCE.

Marcus PI
Microbiology Section, U-44, Univ. Connecticut, Storrs, CN, 06268
Tex Rep Biol Med; 35:336-342 1977

Intrinsic interference, originally observed as a Newcastle disease virus (NDV)-refractory state induced by several types of viruses, is an example of heterologous interference not mediated by interferon action. However, it is not without precedent that taxonomically unrelated viruses initiate similar molecular events, eg, the induction of interferon production, or the inhibition of host-cell macromolecular synthesis. Such observations prompt a search for a viral reactant produced in common. In the case of intrinsic interference heterologous polymerases were postulated to represent the molecular species shared in common. The NDV (or detector virus)-refractory state arises only in those individual cells of a population actually infected by the inducing virus, and presumably results from the action of proteins (polymerases?) coded for by the viral genome. Thus, intrinsic interference differs fundamentally from that mediated by an extrinsic protein, interferon, coded for by the cell genome. Only test conditions rigorous enough to exclude the action of interferon allow an unambiguous assignment of intrinsic interference to an antiviral state. Three such tests are suggested: the use of (i) actinomycin D as an inhibitor of host-cell RNA synthesis, (ii) cells inherently refractory to interferon induction (like Vero green monkey kidney cells) or action, and (iii) specific antibody to interferon. Clearly, many complications still attend the interpretation of results involving multicomponent systems of virus-mediated interference. The identification of intrinsic interference as a type of heterologous viral interference not-mediated by interferon may serve to minimize these complications and help shed light on an exciting area of research capable of providing new and insightful approaches to viral bio- and chemotherapy. (Author abstract) (27 Refs)

295. CELL KILLING BY VIRUSES - SINGLE-CELL SURVIVAL PROCEDURE FOR DETECTING VIRAL FUNCTIONS REQUIRED FOR CELL KILLING.

Marcus PI
Microbiology Section, Univ. Connecticut, Storrs, CT
Adv Pathobiol; (6):192-213 1977

Studies designed to determine whether all, some, or none of the proteins which constitute a virion, or are expressed through its genome, are required for cell killing are reviewed. Of particular consideration is cell killing by the vesicular stomatitis (VS) virus. Experiments are described which attempt to define the requirements for cell killing by VS virus. African green monkey kidney (GMK) cells of the Vero line were used for their unusual attribute of being totally nonresponsive to inducers of interferon. The experiment on virus-cell interaction is fully detailed and based on the single-cell survival test. It is divided into the following sections. (1) Cell-killing particle assay, (2) cell killing by UV radiation and by heat-inactivated wild type vs virus, (3) cell-killing by mutant Ts-G114 (T), (4) time course for acquiring a lethal dose of cell-killing factor, (5) prevention of the expression of cell killing of VS virus by interferon. (42 Refs)

296. COMMON PATHWAYS OF INTERFERON AND HORMONAL ACTION.

Blalock JE, Stanton JD
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Nature (Lond); 283(5745):406-408 1980

Pathways of interferon (IF) and hormonal stimulation of mouse myocardial cell (MMC) and human amnion cell (WISH) cultures were investigated. Both noradrenaline (NA) and mouse IF increased the spontaneous beat frequency of MMC, while human IF had no effect. Mouse IF and NA increased the beat frequency of MMC with similar kinetics; max stimulation with NA or IF required 1 or 2 min, respectively. Overnight treatment with NA produced a dose-dependent development of antiviral activity in MMC; max antiviral activity caused by NA was observed at the same concentration (10(-6) M) as was max stimulation of beat frequency. Overnight treatment with IF also produced antiviral activity in MMC. The continued presence of either NA or IF was not necessary for continued antiviral activity, and actinomycin D blocked the antiviral activity of both compounds. Human IF added to cocultures of MMC and WISH cells caused a dose-dependent increase in the beat frequency of the myocardial cells. This effect was only observed when the myocardial cells were in contact with the human cells. Addition of NA to cocultures that had been maximally stimulated by IF caused no further increase in beat frequency. Both cell types in cocultures in the presence of human IF also developed antiviral activity. It was concluded that IF can have hormonal activity and that hormonal stimulation can result in IF-type antiviral activity. These findings indicated that IF and hormonal action are mediated by common pathway(s) and that such pathways may involve similar secondary messenger molecules. (16 Refs)

297. ALTERATIONS OF A MOUSE MAMMARY TUMOR VIRUS GLYCOPROTEIN WITH INTERFERON TREATMENT.

Yagi MJ, King NW, Bekesi JG
Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, New York, NY, 10029
J Virol; 34(1):225-233 1980

The effects of exogenous mouse interferon on the MJY-alpha mammary tumor cell line chronically infected with mouse mammary tumor virus (MMTV) were examined. Interferon at concentrations of 25 to 2,000 IU/ml in culture medium did not alter the growth rate or morphology of the cell layers. Electron microscopic examination of interferon-treated cells indicated a decrease in the numbers of A-type and budding B-type particles of MMTV. However, the levels of extracellular MMTV virions in the culture supernatants were not significantly reduced. Profiles of MMTV glycoproteins and nonglycosylated polypeptides obtained by sodium dodecyl sulfate-polyacrylamide gel electrophoresis of virions purified from interferon-treated cultures revealed increases in the relative levels of the 60,000-dalton glycoprotein, gp60. (Author abstract) (41 Refs)

298. INTERFERON-MEDIATED INHIBITION OF MOUSE MAMMARY TUMOR VIRUS EXPRESSION IN CULTURED CELLS.

Strauchen JA, Young NA, Friedman RM
Lab. Pathology, NCI, Bethesda, MD 20014
Virology; 82(1):232-236 1977

Interferon (10-100 IU/ml) caused a 5- to 10-fold inhibition of glucocorticoid-stimulated mouse mammary tumor virus expression in a murine mammary tumor cell line, Mm5m+/c1. Possible mechanisms of action are discussed and compared with mechanisms reported for interferon inhibition of murine leukemia virus. (16 Refs)

299. VIRUS-SPECIFIC EFFECTS OF INTERFERON IN EMBRYONAL CARCINOMA CELLS.

Nilsen TW, Wood DL, Baglioni C
Dept. Biological Sciences, State Univ. New York at Albany, Albany, NY, 12222
Nature (Lond); 286(5769):178-180 1980

The effects of mouse interferon on the infection of PCC4 mouse embryonal carcinoma (EC cells) by picornaviruses was investigated. A dye uptake method was used to measure virus synthesis. A 20-hr treatment with interferon (100 units/ml) just before viral infection, inhibited the replication of mengo virus, encephalomyocarditis virus (EMCV), and two temperature-sensitive (ts) mutants of vesicular stomatitis virus (VSV), tsG114 and tsG11. However, a higher concentration of interferon (300 units/ml, 20 hr) did not inhibit the replication of wild-type VSV, Sindbis virus, or influenza virus. Additional experiments, in which the number of plaque-forming units produced by viral infection was measured, confirmed that interferon (100 units/ml, 20 hr) reduced the EMCV titer by approx 1,000) but not the VSV-titer. The protective effect of interferon in the EC cells is therefore clearly virus-specific. (27 Refs)

300. EFFECT OF INTERFERON ON MURINE THYMIC LYMPHOMA CELLS IN VITRO (MEETING ABSTRACT).

Yokota Y, Nakai M, Kawamata J, Kishida T
Dept. Microbiology, Osaka Medical Coll., Takatsuki-shi, Osaka Prefecture 569, Japan
Proceedings of the 38th Annual Meeting of the Japanese Cancer Association held in Tokyo, Japan, September 1979. Japanese Cancer Association, Tokyo, Japan, 329 pp., 1979.

Mouse brain interferon (MB-IF) was added to the serially transplanted mouse leukemia cell line established from thymic lymphoma induced with Gross passage A virus for comparison of growth with that of untreated cells. When 50-1,000 IU of MB-IF/ml was added 1x in the initial culture stage, cell growth was inhibited in proportion to the concentration, but its duration was short, cells beginning to grow 2-3 days later and rapidly reaching a growth rate similar to that of the untreated cells. When MB-IF was added 3x, 1x in the initial stage and 2x at 2-3 day intervals, the cell growth was more strongly inhibited than by single administration in the initial stage. MB-IF exerted no cytocidal effect. The microstructure of leukemia cells treated with MB-IF and the course of growth and budding of C-type virus were compared with those of the untreated cells. (no Refs)

301. ANTIVIRAL AND CELL MULTIPLICATION INHIBITORY ACTIVITIES OF MOUSE INTERFERON PREPARATIONS TESTED ON AN INTERFERON SENSITIVE MURINE SARCOMA CELL LINE.

Degre M
Kapt. W. Wilhelmsen og Frues Bakteriologiske Institutt, Univ. Oslo, Rikshospitalet, Oslo, Norway
Acta Pathol Microbiol Scand [B]; 88(4):219-223 1980

The cell multiplication inhibitory effect of SDS-treated mouse interferon separated into antiviral (AV) and cell multiplication inhibitory (CMI) fractions was compared to that of untreated similar interferon on a line of murine osteosarcoma cells. The untreated interferon preparation and the CMI fractions dose-dependently inhibited the multiplication of the cells as measured by cell count and incorporation of 3H-thymidine into the cultures. The AV fractions, containing comparable antiviral activities as the untreated interferon preparations, had only a minor effect on cell multiplication. The biochemical properties of the fractions studied remain unknown. (Author abstract) (19 Refs)

302. AN INTERFERON-SENSITIVE STEP EARLY IN THE ESTABLISHMENT OF INFECTION OF MURINE CELLS BY MURINE SARCOMA/LEUKAEMIA VIRUS.

Morris AG, Burke DC
Dept. Biological Sciences, Univ. Warwick, Coventry CV47AL, England
J Gen Virol; 43(part1):173-181 1979

NIH3T3 mouse cells were infected at very high multiplicity with murine sarcoma/leukemia virus (MSV/MLV) and then cloned. All of the 48 clones obtained were morphologically transformed, all but one showed anchorage-independence of growth, typical of MSV-transformed NIH3T3 cells and most (91%) produced MSV/MLV. When cells pre-treated with 10(4) units/ml of purified interferon (IF) were infected under the same conditions and then cloned in the presence of the same amount of IF, only 6/63 clones were morphologically transformed. The remaining clones showed a degree of anchorage-independence typical of the uninfected parental cells and very few (2.4%) produced virus. Furthermore, the MSV genome could not be rescued in any of the 23 clones tested and only 1/10 clones produced tumors. The properties of these clones remained stable over a period of 10 to 20 passages in the absence of interferon. It is concluded that interferon can irreversibly block an early step in the MSV/MLV infectious process. (21 Refs)

303. EFFECT OF INTERFERON ON MURINE VIRUS INFECTION. III. EFFECT OF INTERFERON ON MSV-INDUCED TRANSFORMATION.

Pitha PM, Staal SP
Oncology Center, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Virology; 90(1):151-155 1978

The effect of interferon on viral transformation has been examined in a system where helper leukemia virus is not required for focus formation. This allows investigation of the effect of interferon on sarcoma virus function. No alteration in the morphology of foci was observed. A small (approx 50%) reduction in the number of foci was observed with concentrations of interferon that did not affect cell growth. This reduction was observed only when interferon was present early in infection. (Author abstract) (19 Refs)

304. EFFECT OF PROLONGED INTERFERON TREATMENT ON MOUSE EMBRYONIC FIBROBLASTS TRANSFORMED BY MURINE SARCOMA VIRUS.

Chany C, Vignal M
Nat. Inst. Health Med. Res., Paris, France
J Gen Virol; 7(3):203-210 1970

BALB/c mouse embryonic fibroblasts, transformed by Moloney sarcoma virus (MSV) and grown in the presence of interferon (IF+), differed from the original MSV cells in that epithelial cells were more prominent than spindle-cells, contact inhibition reappeared, and there were 10-fold more Type C particles, but the Moloney transplantation antigen and the group antigen persisted. When interferon was omitted for 30 passages (IFo), the cells retained morphological, growth and antigenic characteristics, but a greater number gave rise to colonies in soft agar. The MSV-IF+ cells were least sensitive to exogenous interferon, and MSV-IF+ and IFo cells, after challenge with Newcastle's disease virus, produced 10-fold more interferon than the original MSV cells, with no refractory state.

305. INHIBITORY EFFECT OF INTERFERON PREPARATIONS ON THE INDUCTION OF ENDOGENOUS MOUSE TYPE-C VIRUSES BY IODODEOXYURIDINE (IUDR).

Blaineau C, Kishida T, Salle M, Peries J
Inst. Recherches Leucemies, Lab. Hematol. Exp., Hop. Saint-Louis, Paris, France
IRCS Med Sci: Cancer; 3(5):258 1975

The effect of mouse interferon on the activation of endogenous type-C viruses by iododeoxyuridine in BALB/c mouse cells (sarcoma virus-transformed, line Ki-BALB) was studied by incubating the cells with interferon (100 NIH international reference units/ml) for 8 hr prior to and during treatment with iododeoxyuridine. Mouse interferon from several sources (brain, tissue culture, and serum) inhibited virus production 87-97%. The effect was proportional to the amount of activity in various preparations and was neutralized by antibody specific for mouse interferon. Activity was lost by heating for 1 hr at 60–C and by trypsin treatment. Activity was retained after 3 d at pH 2. Mock mouse interferon preparations were inactive, as was human interferon. It is suggested that interferon could be used in human leukemic pts to impede the expression of hypothetical endogenous oncornaviruses. (5 refs)

306. SUPPRESSION OF MURINE LEUKAEMIA VIRUS PRODUCTION BY OUABAIN AND INTERFERON IN MOUSE CELLS.

Tomita Y, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
J Gen Virol; 38(2):223-230 1978

The effects of ouabain on the production of murine leukemia virus (MuLV) by K3b and JLS-V9 cells were determined. Addition of 0.1 mM ouabain reduced virus yield from both K3b and JLS-V9 cells by greater than 50% and 0.5 mM ouabain reduced it by 93% and 89%, respectively, as determined by particle-associated reverse transcriptase activity. However, intracellular reverse transcriptase activity was not altered. Ouabain also reduced the growth rate of these cells up to 81% at a concentration of 0.4 mM. Experiments with 0.5 mM ouabain indicated that MuLV production decreased more rapidly than protein synthesis. K3b cells were also treated with 100 units/ml interferon and 0.5 mM ouabain to determine whether the antiviral action of the former is blocked by the latter. Mouse interferon blocked MuLV production and was not affected by simultaneous ouabain treatment. (23 Refs)

307. INTERFERON INHIBITION OF AUTOGENOUSLY INDUCED VIRIONS (C PARTICLES) IN SYNCHRONIZED L-929 CELL CULTURES.

O'Shaughnessy MV, Easterbrook KB, Lee SH, Katz LJ, Rozee KR
Dept. Microbiol., Dalhousie Univ., Halifax, Canada
JNCI; 53(6):1687-1690 1974

The effect of mouse interferon on the growth rate of L-929 cells was determined. Control cultures had doubling times of 15 hr. Incorporation of 400 U of interferon/ml into the culture medium increased the doubling time to 25 hr. The growth rate returned to that of control when the interferon was removed, even following five days exposure to high concentrations. The antiviral action of interferon was not reversible; viral replication was inhibited for a time equivalent to three to five cell generations following interferon removal. Interferon also delayed DNA synthesis and mitosis in synchronously growing cells. Interferon significantly decreased the production of C-type virions which was at its peak during metaphase in control cultures. In this culture system, the anticellular and antiviral activities of interferon appear to be separable phenomena.

308. PHYSICAL MORPHOLOGICAL, AND BIOCHEMICAL ALTERATIONS IN THE MEMBRANE OF AKR MOUSE CELLS AFTER INTERFERON TREATMENT.

Chang EH, Jay FT, Friedman RM
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD, 20014
Proc Natl Acad Sci USA; 75(4):1859-1863 1978

Interferon treatment of AKR,C**- cells was followed by the establishment of an antiviral state and apparently concomitant morphological, physical, and biochemical alterations of the cell plasma membrane. The density of the plasma membrane was significantly altered, and the concentration of some plasma membrane glycoproteins and the number of intramembranous particles observed in freeze-fracture electron micrographs were increased. A parallel increase in the concentration of intramembranous particles and the resistance to viral infection during interferon treatment as well as their parallel decrease upon removal of interferon suggests a relationship between the particle density and the establishment of the antiviral state. (Author abstract) (28 Refs)

309. INTERFERON INHIBITS INDUCTION OF ENDOGENOUS MURINE LEUKEMIA VIRUS PRODUCTION.

Ramseur JM, Friedman RM
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, and Digestive Disease, NIH, Bethesda, MD 20014
Virology; 73:553-556 1976

Interferon inhibition of the production of endogenous murine leukemia viruses (MuLV) was studied in Kirsten sarcoma virus (KSV)-transformed Balb/3T3 cells (KBalb/3T3), SV40-transformed Balb cells, and AKR mouse embryo cells. Interferon inhibited expression of MuLV from 5-iododeoxyuridine (IUDR)-exposed KBalb/3T3 cells or AKR cells; inhibition was more marked with AKR cells. Viral expression was measured by a reverse transcriptase assay. In this study, KBalb/3T3 cells were treated with cycloheximide up to 16 hr after exposure; this treatment induced production of only xenotropic (X)-tropic viruses, which could not re-infect the cells. Treatment 16 hr previously with interferon (3-100 units/ml) caused a concentration-dependent reduction of virus production; at 100 units/ml culture medium, KSV foci were reduced by 83%. Hence, the effect of interferon to inhibit virus production is at the stage of viral induction. (9 Refs)

310. PERSISTENCE OF THE VIRAL GENOME IN INTERFERON-TREATED CELLS INFECTED WITH ONCOGENIC OR NONONCOGENIC VIRUSES.

Friedman RM, Costa JC, Ramseur JM, Meyers MW, Jay FT, Chang EH
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD 20014
J Infect Dis; 133(Suppl):A43-A50 1976

When AKR mouse cells which were chronically infected with a murine leukemia virus were treated with interferon (30 international mouse units) for 9 days, a sustained inhibition of extracellular production of murine leukemia virus was observed in the absence of any inhibition of viral intracellular p30 antigen or reverse transcriptase. Removal of interferon resulted in a rapid reversal of these effects. Infectious virus and intracellular viral antigen were rapidly eliminated from interferon-treated (1000 IU) cultures infected with a high multiplicity of herpes simplex virus type 1. In cultures infected with a high multiplicity of vesicular stomatitis virus, titers of virus remained low in interferon-treated (100 IU) cells, but after 2 wk they rose rapidly, and the cultures were destroyed. If treatment with interferon was reinstituted as late as 9 days after primary infection, infectious vesicular stomatitis virus was eliminated, and there was no evidence for survival of the viral genome in these cultures. Although inhibition of virus production by treatment with interferon was possible in cultures infected with murine leukemia virus, the viral genome was not eliminated; in contrast, the viral genomes were apparently eliminated from cultures infected with vesicular stomatitis virus or herpes simplex virus after treatment with interferon. (17 refs)

311. POSSIBLE ROLE OF THE FRIEND VIRUS LIFE CYCLE IN DIFFERENTIATING FRIEND LEUKEMIA CELLS TREATED WITH INTERFERON.

Dolei A, Capobianchi MR, Cioe L, Colletta G, Vecchio G, Rossi GB, Affabris E, Belardelli F
Instituto di Virologia, Univ. Rome, Rome, Italy
Haematol Blood Transfus; 23:307-311 1979

The action of dimethylsulfoxide (DMSO) and interferon (IF) on the growth and differentiation of Friend erythroleukemia cells (FLC), and the effect of IF on the Friend leukemia virus (FLV) genome were investigated. The control of FLC differentiation by IF is reviewed. Under conditions allowing at least 2-3 cell doublings in the presence of DMSO, Hb synthesis was reduced by 90%, but globin messenger (m)RNA only by 30% in FLC treated with DMSO plus IF. IF doses lower than 100 IU/ml induce a substantial increase of Hb-producing cells in DMSO-stimulated cultures; this effect is mediated by an increase of globin mRNA levels. While in DMSO-treated FLC there was a significant increase of viral RNAs, IF treatment alone barely reduced the virus-specific cytoplasmic RNA content. DMSO + IF significantly decreased the viral RNA concentration as compared to untreated and DMSO-treated FLC. These data, apparently unrelated to one another (the peculiar inhibitory action of IF on the life cycle of FLV and the 'pendulum' type of effect on FLC differentiation) are discussed with a possible unifying interpretation. It was suggested that SFFV induces high levels of polycythemia in susceptible mice, playing a critical role in providing lymphatic leukemia virus component (LLV) with a larger subpopulation of 'erythroid-committed' precursor cells, which then become available for the transforming event. An erythroleukemia would ensue as a consequence of a combined and sequential action of the two viruses. It was postulated that LLV is sensitive even at low doses of IF, while SFFV is sensitive only to high doses. (14 Refs)

312. INTERFERON EFFECTS ON FRIEND LEUKAEMIA CELLS. I. EXPRESSION OF VIRUS AND VIRUS AND ERYTHROID MARKERS IN UNTREATED AND DIMETHYL SULPHOXIDE-TREATED CELLS.

Dolei A, Colletta G, Capobianchi MR, Rossi GB, Vecchio G
Istituto di Virologia, Univ. Rome, Rome, Italy
J Gen Virol; 46(1):227-236 1980

The effects of low doses (40 to 1000 units/ml) of mouse interferon (IF) on the expression of Friend leukemia virus (FLV) and globin genes in Friend leukemia cells (FLC) have been examined. IF blocks production of extracellular virus, but virus antigens accumulate in the cytoplasm. In cells treated with IF at the time of seeding, there is a reduction in the amount of RNA specified by the lymphatic leukemia virus (LLV) component of FLV; with the same IF dose there is a small but definite stimulation of Hb and globin messenger RNA synthesis. The effects of IF on LLV gene expression are even more pronounced in dimethyl sulfoxide-stimulated FLC. No correlation was found between LLV gene expression and the appearance of erythroid markers. (Author abstract) (34 Refs)

313. FRIEND VIRUS RELEASE AND INDUCTION OF HAEMOGLOBIN SYNTHESIS IN ERYTHROLEUKAEMIC CELLS RESPOND DIFFERENTLY TO INTERFERON.

Swetly P, Ostertag W
Ernst Boehringer Inst., Vienna, Austria
Nature (Lond); 251(5476):642-644 1974

Interferon inhibits Friend virus release but doesn't interfere with DMSO-induced differentiation, changing neither the time course, the amount of hemoglobin synthesis, nor the number of cells involved. (16 refs)

314. CAT INTERFERON INHIBITS FELINE LEUKAEMIA VIRUS INFECTION IN CELL CULTURE.

Rodgers R, Merigan TC, Hardy WD, Old LJ, Kassel R
Stanford Univ. Sch. Med., Stanford, Cal.
Nature [New Biol]; 237(78):270-271 1972

Interferon was prepared in CrFK (a feline kidney line) cells using Newcastle disease virus and assayed against bovine vesicular stomatitis virus (VSV) by a plaque reduction assay on monolayers of FFc60wf (a feline embryo fibroblast line). FFc60wf monolayer cultures were infected for 5 hr at 37 degrees C with 1 ml of 0.45 microm membrane filtrates of tissue culture supernatant obtained from cells chronically infected with feline leukemia virus (FeLV). Cells were treated with interferon (4 ml) for various times before and after infection and were examined at various times after infection for the presence of viral group-specific antigen, using an indirect immunofluorescence procedure. After 18-hr pretreatment, and on assay 2 d postinfection, FeLV was approx. 1,000x less sensitive than VSV to the action of interferon; the dose-response curve was sigmoidal, and a max of only 80% inhibition of infection was achieved. When cells were pretreated with interferon (17,500 U/4 ml) for 24 hr before infection on d. 0, viral group-specific antigen was reduced by 96, 73, 53, and 42% on d. 1, 2, 3, and 4, resp. When cells were treated with interferon (8,700 U/4 ml) on d. -1, +2, or +4, infected on d. 0, and cultures read on d. 2, 4, and 6, resp, reductions in viral group-specific antigen were 37, 21, and 11%, resp. When interferon (8,700 U/4 ml) remained in the medium for the duration between virus infection and measurement, there was an even greater effect (80% reduction 2 d after infection). In vivo studies on the effect of exogenously prepared interferon on known cases of FeLV-associated leukemia in cats are in progress. (11 refs)

315. DIFFERENCES IN THE ANTIVIRAL AND ANTIONCOGENIC EFFECTS OF INTERFERONS PRODUCED IN PERITONEAL CELLS OF MICE AND IN KREBS-2 ASCITIC CARCINOMA CELLS.

Marchenko VI, Pokidysheva LN, Malinovskaia VV, Aliab'eva TI, Khesin IaE
N. F. Gamaleia Inst. Epidemiology and Microbiology, USSR Acad. Medical Sciences, Moscow, USSR
Vopr Virusol; (3):344-348 1977

Results of the comparative analysis of two murine interferon preparations are presented. Macrophage interferon was derived from mouse peritoneal cells; 'Krebs' interferon, from ascitic fluid of albino random bred mice with transplanted Krebs-2 carcinoma. Interferon synthesis was induced by incubation of the cell cultures with Newcastle disease virus. L cells treated with macrophage interferon developed resistance to vesicular stomatitis virus within 5-6 hr of exposure, while L cells treated with Krebs interferon developed resistance within 1-2 hr of exposure. Activity of acid phosphatase was higher in L cells treated with Krebs interferon (40%, compared with 2% in cells treated with macrophage interferon). Both macrophage and Krebs interferon inhibited reproduction of Krebs-2 carcinoma cells in mice. (3 Refs)

IV. GENERAL REVIEWS ON INTERFERONS' ANTIVIRAL ACTIVITY

316. THE INTERFERON SYSTEM.

Stewart WE
Interferon Lab., Sloan-Kettering Inst. Cancer Res., 1275 York Ave., New York, NY, 10021
The Interferon System. Vienna, Springer-Verlag, 421 pp., 1980.

The vast literature on interferon (IF) that has accumulated over the past 20 yr is condensed into a comprehensive reference book. Among the topics discussed are IF assays, IF inducers, induction mechanisms, the genetics of IF production, IF production, the purification and characterization of IF, the genetics of IF action, mechanisms of antiviral actions of IF, nonantiviral actions, pharmacokinetics, antiviral actions in animals, antitumor activities in animals, and clinical use. (2214 Refs)

317. THE INTERFERON SYSTEM.

Baron S
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
ASM News; 45(7):358-366 1979

A discussion on interferon is presented which includes its production and secretion, mechanism of antiviral action, regulation of the immune response, and antitumor action. (51 Refs)

318. INTERFERON.

Ho M, Armstrong JA
Dept. Microbiol., Grad Sch. Public Health, Univ. Pittsburgh, Pa.
Annu Rev Microbiol; 29:131-161 1975

This is a review of published reports on various aspects of interferon since 1970, and it includes such topics as: mechanism of induction, mechanism of action, hyporeactivity, and applications to man. A tentative scheme of classifying interferon inducers is proposed and two general types of interferon production are distinguished. Type I production follows stimulation with specific, known inducers. These inducers are divided into two classes; Class A inducers (good inducers) frequently produce more than 1,000 U/ml of interferon in either cell cultures or in the bloodstream of animals after i.v or i.p inj. They are often active in ug amounts and seem to have the greatest specific activity of all inducers. In contrast, Class B substances are moderate to poor (< 1,000 U) inducers. Frequently they are active when systemically inj in animals but not in cell cultures. Under type II production, the authors attempt to unify a type of interferon production resulting from specific and nonspecific inactivation of lymphocytes and macrophages. Pharmacologically, interferon is a potent substance with a high therapeutic index. The use of interferon in man is summarized in a table. Antiviral use of interferon inducers in man is also presented in another table. Interferon is species specific, and so human interferon is difficult to make in adequate quantities. Because of the high specific activity, although a small mass of interferon can be effective, the actual overall effect is small. The authors conclude that there are a few test systems in which interferon can completely prevent viral replication, and it is unable to affect established infections. It remains to be seen whether increasing the amount of available human interferon, a technically feasible goal, can overcome these problems. (289 refs)

319. INTERFERONS.

De Maeyer E, De Maeyer-Guignard J
Institut Curie, Universite de Paris-Sud, Campus d'Orsay, Bat. 110, 91405-Orsay, France
Virus-Host Interactions: Immunity to Viruses. Fraenkel-Conrat H, Wagner RR, ed. New York, Plenum Press, Comprehensive Virology, Vol. 15, 292 pp., 1979.

Those aspects of interferons that relate to virology are reviewed. Within a given animal species, the heterogeneity of interferons can be ascribed to the presence of several genes for interferons and to different degrees of glycosylation of interferons. Spontaneous synthesis of interferon is unusual. Normally, it is induced by viruses in any nucleated cell of the organism (Type I interferon) or by renewed contact of sensitized T cells with an antigen (Type II). Interferons represent the first line of defense of the organism against viral infection. In addition to their direct anti-viral effect, however, they have modulating effects on various specialized functions of the immune system, such as antibody formation and cell-mediated immunity. (446 Refs)

320. INTERFERON (A BIBLIOGRAPHY WITH ABSTRACTS).

Harrison EA
Natl. Technical Information Service, Springfield, VA
Interferon (A Bibliography with Abstracts). Available Through National Technical Information Service, Springfield, Va., as NTIS/PS-79/0559/9GA:, NTIS/PS-79/0559, 238 pp., 1979.

The cited reports discuss research on interferon inducers; production in tissue and WBC cultures; assay methods; and antiviral activity. (This updated bibliography contains 232 abstracts, 8 of which are new entries to the previous edition). (Author abstract)

321. INTERFERONS AND INDUCERS IN VIVO.

Stebbing N
Res. Div. Searle, High Wycombe, England
Nature (Lond); 279(5714):581-582 1979

The mode of action of interferons at the molecular level is discussed with emphasis on the importance of host factors that are necessary for their effectiveness in the treatment of viral infections. Recent reports are cited that indicate that,

in vivo, WBC interferon at least, has antiviral effects by means other than the known molecular mechanisms. However, the need to know the extent to which observed antiviral effects are due to interferon induction is stressed, since non-interferon mediated antiviral effects of polynucleotides have always been a possibility. Supportive evidence is presented in favor of interferon as sole mediator of antiviral/antitumor effects of polynucleotides. Other possible mechanisms of antiviral effects involving inhibition of protein synthesis by double-stranded polynucleotides and interference with virus replication without production of interferons are discussed. (12 Refs)

322. INTERFERON AND INTERFERON INDUCERS.

Metz DH
Natl. Inst. Medical Res., Mill Hill, London, England
Adv Drug Res; 10:101-156 1975

The mechanism by which a virus induces the synthesis of interferon, the purification and properties of the substance, the mechanism by which it renders a cell resistant to viral infection, and the possibilities for the therapy of virus diseases are reviewed. Viruses and double-stranded polynucleotides induce interferon synthesis both in cell culture and in animals. There are a variety of other organisms and substances which, when injected iv or ip in large doses, induce interferon synthesis in animals only. It is suggested that the reason for the absence of activity in cell cultures is that the cells which respond to these inducers do not attach to glass or plastic and are not readily cultured. There is also evidence, however, that many of these inducers act only on cells of the lymphoreticular system, which is responsible for the organism's immune response. A variety of other microorganisms, such as bacteria, protozoa, Rickettsiae, and chlamydia, also induce interferon synthesis. Some synthetic anionic polymers and copolymers including polyacrylic acids and polymethacrylic acids, maleic anhydride copolymers and polyvinyl sulfate also induce interferon synthesis. The requirements for interferon-inducing ability are a stable long-chain backbone on which negatively charged groups are placed in a regular and dense sequence. A recently discovered class of low molecular wt inducers is typified by tilorone hydrochloride. Three possibilities are suggested to explain the viral induction of interferon: double stranded RNA synthesized by the virus may be the active inducing factor; there are intracellular receptors for a number of types of viral macromolecules and interaction between any receptor and the appropriate substrate may be sufficient to trigger interferon synthesis; and interferon is produced as a nonspecific response to intracellular toxic material. Available evidence seems to indicate that the effect of interferon is the inhibition of specifically viral, and not cellular, macromolecular synthesis in infected cells. There is also evidence that both virus transcription and translation may be inhibited, depending on the virus-cell system examined. It is concluded that, in view of the apparently negligible toxicity of interferon preparations, especially when contrasted with other models of cancer chemotherapy, the use of highly purified human interferon in controlled trials in patients with cancer seems to be warranted. (140 refs)

323. INTERFERON AND INTERFERON INDUCERS.

Rassiga-Pidot AL, McIntyre OR
Cancer Medicine. Holland JF, Frei III E. Philadelphia, Lea and Febiger, 2018 pp., 1973.

Interferon and interferon inducers have been beneficial both prophylactically and therapeutically in many viral and nonviral animal tumor systems. The mechanism of action, not yet clearly defined, may include interference with replication of an oncogenic virus, a direct chemotherapeutic effect, and a stimulation of the immune system. Interferon inducers are used in clinical tests because of the unavailability of large quantities of human interferon; poly I:C has been the most promising, and although clinical testing is still in the early stages, the concepts and principles involved in its use against cancer suggest a useful role in the future. (56 refs)

324. ACTUAL RESULTS AND PROBLEMS OF INTERFERON RESEARCH.

Zschiesche W
Zentralinstitut fur Molekularbiologie, Akademie der Wissenschaften der DDR, Lindenberger Weg 70, DDR-1115 Berlin-Buch, E. Germany
Dtsch Gesundheitsw; 35(41):1609-1618 1980

Interferons are heterogeneous glycoproteins. Three molecular species with distinct biochemical, physicochemical and antigenic properties have been identified: leukocyte interferon (Le-IF), fibroblast interferon (F-IF), and immune interferon. Interferons can be induced by a number of different agents, among them viruses, double-stranded RNA and analogues, polyanions, fluorenone derivatives etc. Immune interferon, on the other hand, is generally liberated in the course of cell-mediated immune reactions. Although, in principle, all cell types have been found to be capable of generating interferons in vitro, formation in vivo is mainly based on the activity of mononuclear phagocytes and lymphocytes. Interferons have been shown to exert a so-called pleiotropic effect. The most pronounced activities at the cellular level are: induction of antiviral resistance, inhibition of proliferation, activation of macrophages and lymphocytes, alteration of cellular membranes, release of histamine and mediators of inflammation. The following organismic effects result: antiviral activity, antitumor activity, modulation of immune responsiveness, antimicrobial activity, inflammatory activity. In the last yr, methods for large-scale production of interferons have been developed by mass cultivation of induced cells. Likewise, possible synthesis by means of genetic engineering has lately been described. Thus, the basis for broad clinical trials is provided. With the limited amounts of Le-IF available up to now, considerable therapeutic effects have already been reported, particularly in herpetic keratitis, chronic aggressive hepatitis and osteogenic sarcoma. In spite of our hitherto poor understanding of the mode of action and of the pharmacology of interferons, these substances may be expected to be promising agents in the therapy of viral, tumor and possibly of immune diseases. (Author abstract) (188 Refs)

325. TWENTY YEARS AFTER THE DISCOVERY OF INTERFERON: THE PROGRESS AND THE PERSISTENT PROBLEMS.

Borecky L
Inst. Virology, Slovak Academy Sciences, Bratislava, Czechoslovakia
Acta Biol Med Ger; 38(5/6):709-731 1979

The historical aspects of interferon research are reviewed, and the mechanism of interferon action is discussed in detail. Immune effects of interferon, its inducers, and perspectives of the therapeutic exploitation of interferon also are considered. (134 Refs)

326. INTERFERON TWENTY YEARS LATER.

De Maeyer E
Fondation Curie-Institut du Radium, Universite de Paris-Sud, 91405 Orsay, France

Bull Inst Pasteur; 76(4):303-324 1978

The current status of interferon research is discussed with a focus on experiments using mouse and human interferon. The purification of mouse interferon, interferon mRNA, interferon production in mice, and cell-mediated immunity are reviewed. (130 Refs)

327. ON THE VARIED BIOLOGICAL EFFECTS OF INTERFERON.

Gresser I
Institut de Recherches Scientifiques sur le Cancer, B.P. 8, 94800 Villejuif, France

Cell Immunol; 34(2):406-415 1977

The biological effects of interferon, their relevance to the immune response, and why interferon elicits disparate effects are presented. Biological effects of interferon on cells include antiviral activity, inhibition of cell division, enhancement of cell function, and effects on cell surface. Interferon also interacts with the immune system by inhibiting antibody response on B lymphocytes, but does not inhibit macrophage or T cell-helper functions. The addition of interferon several days after antigen stimulation results in an increase in the number of plaque-forming cells. Speculations on the biologic significance of the varied effects of interferon on cells include the comparison of behavior of dividing and nondividing cells in terms of cell function, expression of histocompatibility antigens, and susceptibility to viral multiplication. It appears that interferon exerts multiple effects on cells, and that these effects are not as unexpected and as unrelated as once thought. (135 Refs)

328. ELECTROPHORETICALLY PURE MOUSE INTERFERON EXERTS MULTIPLE BIOLOGIC EFFECTS.

Gresser I, De Maeyer-Guignard J, Tovey MG, De Maeyer E
Institut de Recherches Scientifiques sur le Cancer, B. P. 8, 94800 Villejuif, France

Proc Natl Acad Sci USA; 76(10):5308-5312 1979

Partially purified (PP) and electrophoretically pure (EP) mouse interferon (IF) from C-243 cells had species-specific antiviral activity. EP-IF contained two proteins (mol wt 22,000 and 35,000). The specific activity of PP-IF was 1-2.9 x 10(7) reference units/mg protein, compared to 9.9 x 10(8) to 1.5 x 10(9) units/mg for EP-IF. EP-IF was stabilized by suspension in bovine serum albumin (BSA: 100 ug/ml in phosphate-buffered saline). PP-IF or EP-IF (9-day ip course) was given to BALB/c mice, beginning 2 hr after ip inoculation of Ehrlich carcinoma (1.6 x 10(4) cells). The mean survival time (MST) was 16.7 days in untreated controls, with no long-term survivors (LTS: greater than 160 days). BSA alone (0.25 ml/day) had no antitumor effect. Both IF preparations significantly increased the MST (34.2 days with EP-IF, 51.3 days with PP-IF) and the LTS rate (1/8 and 3/7 mice, respectively), and significantly reduced tumor cell counts (day 7 after tumor inoculation). There was no significant difference between the antitumor effects of PP-IF and EP-IF. EP-IF significantly inhibited the multiplication of IF-sensitive L1210 mouse leukemia cells, but not of an IF-resistant subline. L1210 cells exposed to EP-IF absorbed more mouse alloantiserum (C57BL/6 mouse anti-DBA/2 lymphocyte serum) than untreated or BSA-exposed L1210 cells. Both IF preparations also inhibited antibody formation (in vitro), sensitization to sheep RBC (in vitro), and the expression of delayed-type hypersensitivity (in mice). Both IF preparations enhanced natural killer cell activity (in vitro and in vivo), the sensitivity of mouse embryo fibroblasts to polyinosinic:polycytidylic acid (poly-I:poly-C) in vitro, and IF production induced by poly-I:poly-C. These results suggest that the molecules responsible for the antiviral activity of IF are also responsible for these other biologic effects. (60 Refs)

329. THE COMPARATIVE BIOLOGY OF IMMUNE AND CLASSICAL INTERFERONS.

Epstein LB
Cancer Res. Inst., Univ. California, San Francisco, CA, 94143

Biology of the Lymphokines. Cohen S, Pick E, Oppenheim JJ, ed. New York, Academic Press, 626 pp., 1979.

Similarities and differences between classical and immune interferon (IF) are compared with regard to production, characterization, assay, mechanism of action, role as an antiviral agent, effects on the immune response, and other nonantiviral effects. Immune IF is produced by immune-stimulated WBC, while classical IF is produced by diverse cell types, including WBC. Clinical studies in which either the production of IF as a measure of the competence of the producing cell type or the use of classical IF as a therapeutic agent were investigated are described. The following principles concerning IF are emphasized: 1) heterogeneity; 2) diverse biological effects aside from antiviral activity; 3) IF as an integral part of the immune response; 4) induction of IF by agents other than viruses; 5) production of IF by cells other than those in the reticuloendothelial system; 6) factors that influence the type of IF produced in response to a given stimulus; and 7) clinical applications of IF for treatment of viral infections associated with malignancy and for malignancy itself. (325 Refs)

330. IMMUNE INTERFERON: SOME PROPERTIES AND FUNCTIONS (MEETING ABSTRACT).

Baron S, Blalock JE, Dianzani F, Fleischmann WR, Johnson HM, Georgiades JA, Stanton GJ
Univ. Texas Medical Branch, Galveston, TX

Abstracts of a Conference on Regulatory Functions of Interferons, held in New York, October 23-26, 1979. New York Academy of Sciences, New York, NY, pp. 11, 1979.

Immune interferon (type II) is produced with other lymphokines by T lymphocytes stimulated by mitogens or by antigens to which they are sensitized. It may function as an antiviral, antitumor and immunoregulatory agent. Relatively large amounts of both mouse and human immune interferons are produced in WBC cultures stimulated with the T lymphocyte mitogen, staphylococcus enterotoxin A. Six hundred-fold purification has been achieved using a series of procedures. Antibody to mouse immune interferon distinguishes it from virus-induced and lipopolysaccharide-induced interferons. Unlike virus-induced interferons immune interferon preparations activate cells slowly; it may induce an intermediary cellular protein before inducing the antiviral protein; it exhibits highly potent antitumor cell activity even when partially purified; and it can potentiate the antiviral action of virus-induced interferons. Like virus-induced interferons, immune interferons cannot only activate antiviral activity in cells but also cause the activated cells to transfer their activity to neighboring cells. In addition to immune interferon, a potent inhibitor of all interferons has been identified in lymphokine preparations. (no Refs)

331. THE INTERFERONS AND THEIR SIGNIFICANCE FOR PROPHYLAXIS AND TREATMENT OF HUMANS AND ANIMALS.

Selbitz HJ, Scheel H, Vogt A, Schonherr W
Wissenschaftsbereich Mikrobiologie und Tierseuchen, Sektion TV der KMU, Marg.-Blank-Strasse 8, DDR-7010 Leipzig, E. Germany
Z Gesamte Inn Med; 35(23):837-841 1980

Properties, induction and synthesis, mechanism of action, and medical applications of interferon (IF) are reviewed. Physical properties, enzymatic sensitivity, activities, and species specificity of IF are described. Inducers of IF are listed; these include viruses, nonviral nucleic acids, bacteria, fungal extracts, synthetic polynucleotides, globulins, low-mol wt substances, and polymers. A scheme for IF induction in vivo, IF synthesis, and IF action is outlined. Medical uses of IF are considered with regard to two forms of application: passive (application of IF itself) and active (application of IF inducers). Effects of IF on the host's natural defense mechanisms are discussed, and possible means of improving the pharmacokinetic qualities of IF are suggested. It is noted that current evaluations of clinical applications of IF have primarily involved treatment of respiratory infections and tumors. Results obtained in IF trials in patients with influenza, in patients who underwent surgery for treatment of osteosarcoma, and in hepatitis patients are summarized. It is concluded that experience to date indicates that continued clinical trials of IF are warranted. (46 Refs)

332. THE MECHANISM OF ACTION OF INTERFERON.

Metz DH
Div. Virology, Natl. Inst. for Med. Res., London, England
Cell (Camb); 6(4):429-439 1975

The nature of interferon is briefly summarized, and its mechanism of action is reviewed in five parts: the nature of the extra- and intracellular events leading to the establishment of the antiviral state; the stages in the replication cycle of the virus that is blocked in the interferon-treated cell; in vitro systems displaying an interferon effect; the question of discrimination between viral and host cell metabolism; and the molecular basis for inhibition. Maintenance of the antiviral state apparently requires the presence of the nucleus, particularly with human chromosome 21. It has long been suggested that the site of interferon action is likely at the level of viral protein or RNA metabolism, but in spite of much study on this question, results have been contradictory, and it is difficult at present to draw any firm conclusion regarding the primary site of action. In recent years, considerable progress had been made in developing appropriate cell-free in vitro translational systems which display interferon-mediated inhibition, and a start has been made in developing transcriptional systems. Available evidence seems to argue against the notion that cellular and viral macromolecular synthesis are switched off in the interferon-treated infected cell, and tends to support the concept of discrimination between viral and cellular metabolism. Any proposed mechanism of action must take into account discrimination, the broad spectrum of antiviral action, and the failure of virus resistance to arise. A difference between viral and host mRNAs in the affinity for ribosome attachment with resultant different rates of formation of initiation complexes may be the basis for the molecular action of interferon. (78 refs)

333. MOLECULAR MECHANISMS OF INTERFERON ACTION.

Ball LA
Biophysics Lab. and Biochemistry Dept., Univ. Wisconsin, 1525 Linden Drive, Madison, WI, 53706
Med Pediatr Oncol; 9(1):83-88 1981

The mechanism of interferon action is reviewed in relation to the specific type of interferon (alpha, beta, or gamma) and its specific action. Interferon-inducible genes that code for three enzymes (a protein kinase, 2',5'-oligoadenylate synthetase, and 2-phosphodiesterase) and their effects on the biological activities of interferons are discussed. It is concluded that the known interferon-inducible enzymes appear to be independent elements in a multicomponent defense mechanism by which interferon can protect cells against virus infection, and that the contribution of each element to the overall antiviral state varies from one virus-cell system to another. (30 Refs)

334. ACTIVATION BY INTERFERON OF THE EVENTS LEADING TO THE ANTIVIRAL STATE.

Dianzani F, Baron S
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Tex Rep Biol Med; 35:297-306 1977

Currently, there is sufficient information to outline some of the variables which govern the induction of interferon (IF) of the antiviral state. It may reasonably be concluded that the first critical events which activate the cell response to IF occur at the cell membrane. Binding of IF to receptors on the cell surface is well documented. The finding that prior binding of IF at O C which does not induce resistance but inhibits the action of a second dose of IF at 37 C indicates that the cellular site of activation by IF has highly specific requirements for activation. The additional findings that the kinetics of cellular activation by IF are more rapid and more complex than those of binding, and that this activation proceeds in the absence of the continuous presence of bound IF indicates that the amount of cell-bound IF does not always correlate with activation. It is possible that a fraction of the bound IF activates the cell. It remains to be determined whether the very small amounts of IF bound to cells during the few minutes required for activation account for activation or whether a still smaller fraction of IF reacts with the specific receptor sites. It may also be concluded that the activating reaction is a short-lived (minutes) and temperature dependent event as opposed to the non-activating binding which is longer-lived and may occur at O C. These mechanisms may be related to those which govern the activity of some polypeptide hormones. The first production of the antiviral protein(s) takes place about 30 min after the activation and it does not require the synthesis of intermediary proteins. The intracellular events occurring between the activation and the genetic derepression of the antiviral protein(s) are still obscure. The hypothesis that microtubules may be involved in these processes appears worth pursuing. (Author abstract) (23 Refs)

335. ANTIVIRAL ACTIVITY OF INTERFERONS.

Friedman RM
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, Bethesda, MD 20014
Bacteriol Rev; 41(3):543-567 1977

Studies of the antiviral activity of interferons are reviewed and discussed. In the presence of interferon, cells develop an antiviral state, and a wide variety of viruses do not grow well in these cells. The known facts regarding the induction of the antiviral state are presented. It is suggested that a

small portion of the interferon acts directly on the cell rather than on steps involved in virus multiplication. The interferon receptors appear to be gangliosides or ganglioside-like structures with an oligosaccharide moiety at the functional binding site. Interferon effects on the plasma membrane are discussed. The development of the antiviral state probability requires the intracellular production of an antiviral substance. Four theories about interferon action that are currently accepted are discussed. Evidence is presented that interferon inhibits the following: virus uncoating, transcription of the viral genome, viral protein synthesis, and terminal events in the replication cycle of murine leukemia viruses. Each of these theories is critically analyzed. In simian virus 40 (SV40)-transformed mouse cells, the production of SV40 T-antigen was insensitive to interferon treatment despite the fact that such treatment made the cells resistant to vesicular stomatitis virus infection. Possible explanations for this reaction are presented. (144 Refs)

336. INTERFERON: THE ANTI-VIRAL PUZZLE.

Metz D
Medical Res. Council, Natl. Inst. Medical Res., Mill Hill, London, England
New Sci; 68(974):328-336 1975

The anti-viral substance interferon is reviewed. Interferon is a protein manufactured in virus-infected cells which, when applied to uninfected cells, renders them resistant to subsequent virus infection. The resistance is not virus-specific but is species specific. Interferon is not toxic to cells or organisms. A nasal spray of interferon prevents the common cold caused by rhinovirus infection. Interferon also substantially increases the 5-yr survival of patients with osteogenic sarcoma. Only a few molecules of this glycoprotein are required to protect a cell from virus infection. Double-stranded RNA molecules are potent inducers of interferon synthesis, but this is not a viable approach due to the toxicity of double-stranded RNA. Interferon binds to a receptor on the cell surface; this triggers the synthesis of a new cellular protein (the "antiviral" protein), which acts within the cell to inhibit the replication of the infecting virus. Interferon treated tumor cells are inhibited in growth in vitro and in vivo. It is not clear if the antitumor effect is related to the antiviral effect. Viruses penetrate interferon treated cells, but virus replication is blocked.

337. THE ROLE OF INTERFERON IN VIRAL INFECTIONS.

Sonnenfeld G, Merigan TC
Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Springer Semin Immunopathol; 2(3):311-338 1979

Recent studies on the role of interferon (IF) in mediating the progress of in vivo viral infections were reviewed. The nature of IF, its subclasses, mechanisms of production and action, and relation to the spread of viral infection were discussed. New aspects of IF actions on such nonviral functions as regulation of immune responses, regulation of lymphocyte cell surface antigens and antitumor actions, and also improvement in purification techniques, were outlined. In vitro models for the containment of viral infections by IF, considering types of cytopathic RNA viruses, cytopathic DNA viruses, and oncogenic viruses which are inhibited by application of IF were described. Indirect and direct lines of evidence for an in vivo effect of IF on viral infections were discussed at length. Viruses that are inhibited by treatment of hosts with IF (togavirus, picornavirus, myxovirus, paramyxovirus, rhabdovirus, pox virus, herpes virus), hepatitis infections, in vivo oncogenic virus infections that are inhibited by induction or application of IF to host, and use of anti-IF globulin to demonstrate directly a role for IF in regulating viral infections are surveyed. Actions of IF not directly antiviral which could influence the progress of viral infections, including inhibition of cell division and growth, inhibition of differentiated cell functions, modification of cell membranes, and interactions with the immune system were described. (251 Refs)

338. ANTIVIRAL AGENTS.

Drach JC
Dental Res. Inst., Univ. Michigan, Ann Arbor, MI, 48109
Annu Rep Med Chem; 15:149-161 1980

Drugs active against DNA viruses and broad spectrum antiviral agents are reviewed. Specific topics include inhibitors of herpes simplex virus (HSV) DNA polymerase; inhibitors activated by HSV pyrimidine deoxyribonucleoside kinase; and *interferon*, interferon inducers, and immunomodulators. The current challenge to medicinal chemists is to utilize viral macromolecules as targets for chemotherapeutic agents. (138 Refs)

339. ANTIVIRAL AGENTS.

Baron S, Galasso G
Natl. Inst. Allergy and Infectious Dis., NIH, Bethesda, Md.
Annu Rep Med Chem; 10:161-171 1975

Recent developments in the field of antivirals are reviewed. Improved production techniques have made possible the clinical and animal trials for both *human and mouse interferons*. Studies are also underway to purify interferon (IF) so as to determine its molecular structure and possible methods of synthesis. Large doses of IF have been shown to be prophylactic against respiratory infection when the IF was admin intranasally. The effective intranasal dose has been determined to lie within the range of 800,000 to 14,000,000 U. The mucosal barrier in the nose may be an important factor governing the unexpected requirement for large quantities of IF. In estimating the doses of exogenous IF required in man from tissue culture studies, parenteral admin of 1,000,000 to 1,000,000,000 U of IF may be required depending on viral sensitivity, time of initiation of treatment, and site of infection. Primates have been induced to produce good quantities of IF with resulting protection against certain IF-sensitive viruses. Toxicity and side effects must be considered. Various IF inducers include viruses, propanediamine derivatives, small molecular weight radioprotective chemicals, 9-methylstreptimidone, and biological inducers. (124 refs)

340. THIRD CONFERENCE ON ANTIVIRAL SUBSTANCES.

Herrmann EC
New York Academy Sciences, 2 East 63rd Street, New York, NY 10021
Ann NY Acad Sci; 284:1-720 1976

This is a collection of papers presented at the Third Conference on Antiviral Substances held by the New York Academy of Sciences in February 1976. The agents adenine arabinoside and ribavirin are discussed. Other topics include clinical and biochemical studies of various antiviral substances, as well as the discovery and development of newer antiviral agents. The results of research on tumor viruses and antiviral agents are presented, and the status of *interferon* research is updated. (refs)

341. TRENDS IN RESEARCH AND DEVELOPMENT OF ANTIVIRAL SUBSTANCES.
Becker Y
Lab. Molecular Virology, Hebrew Univ. Hadassah Medical Sch., Jerusalem, Israel
Isr J Med Sci; 11(11):1135-1167 1975

Compounds which show antiviral activity such as those from plants and fungi, synthetic compounds and *interferon* are discussed. The role of metal ions, and semisynthetic and synthetic antibiotics as inhibitors of viral activity is also reviewed. The modification of natural metabolites to compounds that will inhibit viral replication is questioned. (324 refs)

342. ANTIVIRAL AGENTS: ACTION AND CLINICAL USE.
Chang TW, Snydman DR
Infectious Disease Div., New England Medical Center Hosp., Boston, MA
Drugs; 18(5):354-376 1979

The stages of viral replication and the action of antiviral agents are summarized. Immune serum globulins, amantadine hydrochloride, vidarabine, cytarabine, idoxuridine, interferon, and several other antiviral agents are discussed; mechanisms of action, pharmacokinetics, adverse reactions, and clinical trials are reviewed. *Interferon* is considered the most promising antiviral agent due to its broad spectrum antiviral activity and high selectivity against viruses, but the use of interferon is limited because production is by a biological method. (121 Refs)

343. THE PRESENT STATE OF ANTIVIRAL THERAPY.
ter Meulen V
Institut fur Virologie und Immunobiologie, Versbacher Strasse 7, D-8700 Wurzburg, W. Germany
Monatsschr Kinderheilkd; 127(6):367-371 1979

Antiviral therapy using the following agents is discussed: amantadine hydrochloride, thiosemicarbazone, iododeoxyuridine, cytosine arabinoside (Ara-C), adenine arabinoside (Ara-A), ribavirin, and *interferon.* (31 Refs)

344. PROSPECTS FOR CONTROL OF HERPESVIRUS-RELATED DISEASES: A REVIEW.
Merigan TC, Rand KH
Div. Infectious Diseases, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA
IARC Sci Publ; 24(2):947-963 1978

A review is presented of vaccines and other immunoprophylactics for control of herpesvirus-related diseases and of the current status of antiviral chemotherapy and the prospects for other forms of immune enhancement. The many problems and the possible uses of three basic immunoprophylactic regimens pursued today are discussed at length. These regimens are immune globulins to zoster, cytomegalovirus (CMV), and herpes simplex virus (HSV), killed nucleic-acid-free or subunit vaccines, and live attenuated vaccines. Chemotherapies for HSV, CMV, and varicella-zoster virus in use or under study in Europe and the United States are discussed and evaluated. Prominent among them are iododeoxyuridine, adenine arabinoside, and *leukocyte interferon,* but others are included. The control of human herpes viruses will depend upon better understanding of the mode of transmission of these agents between humans, their sites of latency, and the factors that are involved in control both of the severity of primary infection and the frequency of recrudescent disease. Rapid, specific, and, if possible, noninvasive diagnostic techniques must be available early in the course of the disease for optimum therapeutic intervention. (76 Refs)

345. VIRAL LATENCY AND ITS IMPORTANCE IN HUMAN DISEASE.
Tovey MG
Laboratoire d'Oncologie Virale, Institut de Recherches Scientifiques sur le Cancer, 94800 Villejuif, France
Pathol Biol (Paris); 26(10):631-634 1980

The development and reactivation of latent infections by human herpesvirus are discussed in this editorial. The Epstein-Barr virus (EBV) infects only one cell type (B-lymphocytes bearing surface IgM and complement receptors), but can cause either productive or latent infection within that cell. The establishment of a latent EBV infection depends on the cell's stage of differentiation at the time of infection. EBV can be activated by anti-IgM antibodies, protein synthesis inhibitors, halogenated pyrimidines, or 12-O-tetradecanoylphorbol-13-acetate. EBV is distributed worldwide, but EBV-associated tumors (Burkitt's lymphoma and nasopharyngeal cancer) are rare and geographically restricted, suggesting that most persons have an effective host defense against EBV. Acute EBV infections elicit antiviral antibodies, a strong cytotoxic T-cell response (perhaps directed against EBV-induced lymphocyte-detected membrane antigens), and perhaps natural killer cell activity. The reactivation of latent herpes simplex, varicella-zoster or cytomegalovirus infections is often associated with immunosuppressive therapy in cancer patients or renal transplant recipients. Latent infections with EBV and the other viruses persist long after the initial acute infection, even in the presence of a vigorous immune response. The expression of virus-induced antigens may be a determining factor in the host's ability to mount an effective antiviral immunity against latently infected cells. *Interferon* is produced in many situations of latent virus activation, suggesting that it may be involved in the control of virus activation and/or the limitation of subsequent virus replication. Treatment with interferon can reduce the risk of reactivating latent herpesvirus infections in immunosuppressed patients. (15 Refs)

346. THE REGULATION OF ONCOGENIC VIRUSES.
Carter W, Buffett R, Byrd D, Evans MJ, Fjelde A, Horoszewicz J
Dept. Med. Viral Oncol., Roswell Park Mem. Inst., Buffalo, N.Y.
Perspectives in Cancer Research and Treatment; Edited by GP Murphy, D Pressman, EA Mirand (New York, Alan R Liss, Inc):291-300 1973

Progress in regulating the expression of tumor viruses is reviewed. Identification of mycoplasma in human leukemic tissues led to the isolation of a new murine leukemia virus (334C) providing a model system for combined immunotherapy and chemotherapy. Selective inhibition of viral function by interferon and the streptovaricins is discussed, including structural requirements for poly(I;C) as an inducer of interferon, characterization of purified mouse and human interferon, inhibition by streptovaricin of Moloney leukemia virus RNA-dependent DNA polymerase activity, and virus-induced focus formation of BALB/3T3 cells. Studies of hybrid cell populations derived from cloned mouse (RAG) and human (WI-38) cells have revealed production of C-type particles characteristic of RNA tumor viruses and in proportion to human chromosomal content. In attempts to characterize DNA polymerases, which may be involved in the immune response, spleen cell homogenates from immunized and nonimmunized mice have been shown to contain primarily RNA-directed DNA-synthesizing enzyme activity, while studies of Herpes simplex virus-specified synthesis of

thymidine kinase have provided evidence for transfer of a structural gene to mammalian cells in tissue culture. Related ultrastructural investigations of viral morphology are cited. (32 refs)

347. CHAPTER 16. ANTIVIRAL AND ANTITUMOR CHEMOTHERAPY WITH THE INTERFERON SYSTEM.

Levy HB
Natl. Inst. Arth. Infect. Dis., NIH, Bethesda, Md.
Annu Rep Med Chem; 8:150-159 1973

Research developments in the application of interferon, and a number of peripherally related areas are discussed. Studies on the induction and production of interferon, on chemotherapeutic attempts with interferon inducers (tilorone, poly rI:rC, statolon) and interferon in animal systems (including tissue culture), and on therapeutic trials in man are cited and compared. Reports suggest, but do not establish, the possible efficacy of interferon in man. Larger amounts of human interferon or better inducers are needed. Although the toxicity of poly rI:rC is not high, several studies indicate it is not particularly effective in man. Efforts to develop better inducers of interferon as well as to increase production of interferon itself from tissue culture can be expected to continue. (97 refs)

348. NEW TRENDS IN ANTIVIRAL CHEMOTHERAPY.

De Clercq E
Dept. Human Biology, Div. Microbiology, Rega Inst. Medical Res., Katholieke Universiteit Leuven, B-3000 Leuven, Belgium
Arch Int Physiol Biochim; 87(2):353-433 1979

The clinical perspectives and modes of action of 14 antiviral chemotherapeutic agents are reviewed. Interferon and interferon inducers are discussed. (199 Refs)

349. ANTIVIRAL MECHANISMS IN THE CONTROL OF NEOPLASIA.

Chandra P
Center Biological Chemistry, Sch. Medicine, Univ. Frankfurt, Frankfurt, W. Germany
Antiviral Mechanisms in the Control of Neoplasia. Chandra P, ed. New York, Plenum Press, NATO Advanced Study Institute Series, Series A, Life Sciences, Vol. 20, 757 pp., 1979.

An updated view on the genetics of cancer and the role of viruses in cancer, as well as the mechanisms for their control, is presented in a group of meeting papers. The approach to these subjects is interdisciplinary, and the participants included geneticists, epidemiologists, molecular biologists, chemists, virologists, biochemists, pathologists, immunologists, and cell biologists. Techniques are compared and discussed, and results are reviewed with future considerations in mind. Included in the discussion are the basic concepts of oncogenesis by tumor viruses, the role of RNA tumor viruses in human cancer, the role of DNA tumor viruses in human cancer, immunological control mechanisms of neoplasia, molecular approaches to active intervention into oncogenesis by tumor viruses, and the effects of human *interferons* on tumor viruses and on human cancer. (2497 Refs)

350. ANTIVIRAL AGENTS AS ADJUNCTS IN CANCER CHEMOTHERAPY.

Shannon WM, Schabel FM
Kettering-Meyer Lab., Southern Res. Inst. Birmingham, Birmingham, AL, 35205
Pharmacol Ther (Chemother); 11(2):263-390 1980

The association of viruses, viral infections, and cancer and the use of antiviral agents in cancer-treatment programs are reviewed. Acute DNA- and RNA-virus infections associated with cancer and with cytotoxic anticancer therapy are described. The following types of agents that may be used in the treatment of acute infections complicating cancer chemotherapy are examined: purine and pyrimidine nucleoside analogs, thiosemicarbazones, phosphonoacetic acid and phosphonoformic acid, modified polysaccharides, antibiotics and semisynthetic antibiotics, and *interferon* and interferon-inducers. The problem of immunosuppression and antiviral chemotherapy in the compromised host is discussed with respect to immunosuppressive effects of anticancer drugs, effects of oncogenic virus infection on the immune system, and immunosuppressive factors elicited by tumor cells. Evidence of a possible role of viruses in the induction of various human cancers is reviewed, and the rationale for selective inhibition of oncogenic virus replication, viral genomic expression, and virus-induced tumorigenesis is explained. The following antiviral agents with activity against oncogenic viruses are described: purine and pyrimidine nucleoside and nucleotide analogs, narcissus alkaloid extract, ansamycins, template-binding agents, and other inhibitors. Approaches to the search for antiviral drugs that might be useful as adjuncts to cancer chemotherapy are outlined; agents effective against oncogenic viruses or viruses that cuase acute infections in cancer patients are considered. (1126 Refs)

351. TOWARDS TUMOR THERAPY WITH INTERFERONS, PART II. INTERFERONS: IN VIVO EFFECTS.

Krim M
Interferon Evaluation Program, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 55(6):875-884 1980

The in vivo effects of antitumor therapy with interferon are reviewed with regard to their pharmacology and toxicology and their prophylactic and therapeutic effects. The use of interferons as antiviral agents is also discussed. Studies on the antitumor effects of interferons are described for experimental, virus-induced tumors, transplantable tumors, and chemical- and radiation-induced tumors, and in combination therapies. In man, interferon has been used for treatment of patients with classical osteogenic sarcoma, laryngeal papilloma, bladder papilloma, multiple myeloma, leukemias, and metastatic breast cancer. A significant potential role for interferon in the treatment of several common and serious human viral infections has been demonstrated. In animals, mainly the mouse, antitumor effects have been demonstrated with interferon alone. However, regression of gross, palpable tumors has not been achieved in the mouse. In man, antitumor effects have been reported, often including marked tumor regression of both benign and malignant tumors. However, the trials were not prospectively controlled. Toxicity has been minimal. Due to the scarcity of human interferon, an optimum regimen has not been defined. Controlled, expanded trials of interferon in various neoplastic diseases should now be performed. (111 Refs)

352. INTERFERONS AND CANCER.

Friedman RM
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Public Health Service, U.S. Dept. Health, Education, Welfare, Bethesda, MD, 20014
JNCI; 60(6):1191-1194 1978

Studies on the antitumor effects of interferons are reviewed. The antiviral activity of interferons and the site of antitumor activity of interferons are discussed. It is hypothesized that the actions of interferons may be due to a primary effect on the plasma membranes. (49 Refs)

353. COMPREHENSIVE VIROLOGY. VIRUS-HOST INTERACTIONS. IMMUNITY TO VIRUSES.
Fraenkel-Conrat H, Wagner RR
Univ. California at Berkeley, Berkeley, CA
Comprehensive Virology. Virus-Host Interactions. Immunity to Viruses. Fraenkel-Concat H, Wagner RR, ed. New York, Plenum Press, Comprehensive Virology, Vol. 15, 292 pp., 1979.

Immunological reactions to viruses are reviewed in this portion of a compendium of virology. The organization, interactions, and genetic control of the immune system are discussed, as is the measurement of immune responsiveness. Other topics include the immune responses in nonviral and viral systems, immune tolerance in viral systems, and the interactions of viruses with neutralizing antibodies. Humoral immunity to viruses is discussed with reference to the complement system, virus structure, nonimmune non-complement-related humoral viral neutralizing factors, antibody-dependent viral neutralization, antibody- and complement-dependent viral neutralization (lytic and nonlytic mechanisms), and nonimmune complement-dependent viral inactivation. Cellular immunity and the major histocompatibility gene complex (MHC), antigens involved in immune recognition, MHC restriction and immune responsiveness, and the polymorphism of MHC products and MHC-linked susceptibility to disease are also considered. The final chapter deals with *interferons*, including their synthesis, mechanisms of antiviral activity, molecular characterization, interactions with the immune system, and antitumor as well as cell multiplication inhibitory effects. (883 Refs)

354. VIRUSES, INTERFERON AND THE IMMUNE RESPONSE.
Johnson HM
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX
Ill Med J; 157(5):294-299 1980

Interferons have been recognized as having pleiotropic effects which include antiviral, anticellular, immunoregulatory, and antitumor activities. During early stages of cellular viral infection, interferon is produced by transcriptional and translational events. Interferon leaves the cell and reacts with a cell membrane receptor on the producing and surrounding cells. This interaction stimulates the production of antiviral proteins by the cells. These proteins may include a protein kinase that catalyzes the phosphorylation and consequent inactivation of an initiation factor (the IF-2 subunit) needed for protein synthesis, or a polymerase (2'-5' A synthetase) that converts ATP to a 2'-5'-linked oligoadenylate(s) (2'-5'A) in the presence of double-stranded RNA. The 2'-5'A activates an RNA endonuclease that catalyzes RNA degradation. Destruction of messenger RNA by this enzyme inhibits protein synthesis. The interferon system is nonspecific. It is activated by a variety of viruses and produces cellular resistance against a broad range of viruses. Interferon is the earliest of known host defenses, and if experimentally inactivated by anti-interferon antibody viral infections are significantly more severe. Virus-type (type I) interferons, induced by viruses or double-stranded polyribonucleotides, induce interferons produced by fibroblasts and WBC. Lymphoblastoid interferons produced by a transformed human cell line may be a mixture of these interferons. WBC interferon may be induced in some lymphoid cell subpopulations by tumor cells, and may relate both to the antitumor properties of interferon and to a host defense against spontaneous tumors. Immune-type (Type II) interferon is produced by primed T cells after subsequent exposure to the specific antigens, or in unprimed T cells, by T cell mitogens. Type I interferon regulates modulation of the immune response, probably by inducing of a suppressor cell that suppresses B cells, and by killing T killer cells. Null cells are stimulated by this interferon to kill tumor cells. (8 Refs)

355. INTERFERON: ITS INDUCERS AND SOME ASPECTS OF HOST RESISTANCE IN MALIGNANCY.
Merigan TC
Div. Infect. Dis., Stanford Univ. Sch. Med., Stanford, Calif.
Cancer Chemother Rep; 58(4):571-578 1974

The effect of interferon and its possible modes of action were reviewed. Interferon inhibits Rous sarcoma, feline leukemia, Friend leukemia, Rauscher leukemia, Moloney sarcoma, polyoma, Shope fibroma, SV40, adenovirus, and Herpes saimiri viruses in vitro. The therapeutic effect of interferon against spontaneous, chemically-induced, and transplanted tumors was commented upon. The effects were diverse, and the timing of admin critical. Synergy of interferon with BCNU was reported. Clinical studies using interferon were reviewed. In 28 patients treated with interferon (3 x 10 U, 3x wk for up to 2.5 yr), including 5 with Hodgkin's disease, 3 with acute leukemia, 9 with osteogenic sarcoma and 11 with various solid tumors, there were no toxicity or immunosuppressive effects. In 11 patients, interferon admin. (10-50 x 10 U, in 12 hr) was equally effective by the iv or im routes, giving up to 1,000 U circulating for up to 3 d. Work with BCG, pyran copolymer, polyinosinic acid:polycytidylic acid, and other interferon-inducing agents was summarized. Problems in using interferon include the lack of in vitro assays for the prediction of in vivo efficacy, and a lack of understanding of the role of immunity in host resistance to tumors. (65 refs)

356. REPORT OF A WORKSHOP ON STANDARDS FOR HUMAN INTERFERON IN CLINICAL TRIALS.
Attallah AM, Petricciani JC, Galasso GJ, Rabson AS
Bureau Biologics, Food and Drug Admin., Bethesda, MD, 20205
J Infect Dis; 142(2):300-301 1980

The purity, safety, potency and potential correlates of interferon (IF) for clinical performance were topics of discussion at a Workshop on Standards for Human Interferon in Clinical Trials, sponsored by the Food and Drug Administration in October, 1979. Problems concerned with the purification of the glycoprotein were outlined. It was suggested that a specific activity of 10(6) IU/mg of protein be achieved for IF intended for clinical use. In cases where IF is to be used iv, an even higher level of purity and specific activity should be required. Major safety concerns were centered around cell substrates, IF inducers, and possible contaminants introduced into the final product during the stages of purification or production. In the area of potency, the need was recognized for a standardized assay that would be precise, reliable, sensitive, and efficient. The use of a human diploid cell line grown to a contact-inhibitory confluence of one cell thick was recommended. Early studies with IF demonstrated its inhibitory effect in viral infections, and more recent work has shown that IF inhibits tumor cell replication, increases the expression of surface antigens of tumor cells, and enhances host defense mechanisms. (16 Refs)

357. APPLICATIONS OF RADIOIMMUNOASSAY IN THE STUDY OF VIRUSES AND ANTICANCER DRUGS.
Toyoshima S
Div. Chemotherapy, Pharmaceutical Inst., Keio Univ., Sch. Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan
Radioisotopes; 29(5):252-260 1980

The current applications of radioimmunoassay (RIA) for the quantitative study of viruses and anticancer drugs are reviewed. RIA is being used to study quiescent viral infec-

tions, reoviruses, the activity of *interferon* in virus-bearing hosts, the presence of interferon in cells, Type C viruses, protein matrices, and the LD50 of anticancer drugs on host cells and microorganisms. Anticancer drugs are studied with RIA based on the production of antibodies with the anticancer drugs acting as haptens. The haptens that were studied included melphalan, methotrexate, 1-(5-O-succinyl-beta-D-arabinofurasyl) cytosine (ara-C), NaIO4 acidified 5-fluorodeoxyuridine, adriamycin, bleomycin, N-deacetylthiocolchicine, and vinblastine. The studies were performed with hapten-associated antigens in Freund's complete adjuvant or Marcol 52/Arlacel(9.1)-BCGT-Tween 80 injected into rabbits, goats, or monkeys. The conditions of pH, temperature, and other variables influencing the radioimmunoassays of the various anticancer drugs are described. The limits of drug determination with RIA depended on the method of fractionation and ranged from 0.02-0.2 nanog/tube for ara-C to 1-100 nanog/tube for colchicine. (78 Refs)

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